EFFICACY AND SAFETY OF BROMOCRIPTINE QUICK RELEASE AS AN ADD ON THERAPY WITH METFORMIN AND GLIPIZIDE IN TYPE 2 DIABETES MELLITUS PATIENTS- AN OPEN LABEL RANDOMIZED CONTROLLED STUDY

Dissertation submitted to

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY

In partial fulfillment of the

Regulations for the award of the degree of

M.D. (PHARMACOLOGY)

BRANCH - VI

GOVT. CHENGALPATTU MEDICAL COLLEGE

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY

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CERTIFICATE

This to certify that this dissertation entitled "**EFFICACY AND SAFETY OF BROMOCRIPTINE QUICKRELEASE AS AN ADD ON THERAPY WITH METFORMIN AND GLIPIZIDE IN TYPE 2 DIABETES MELLITUS PATIENTS- An OPEN LABEL RANDOMIZED CONTROLLED STUDY"** by the candidate **Dr. M.NITHYAPRIYA** for M.D(Pharmacology) is a bonafide record of the research work done by her, under the guidance of **Dr.S.PURUSHOTHAMAN M.D.** Professor, the Department of Pharmacology, Chengalpattu Medical College, during the period of study (2014- 2015), in the Department of Pharmacology, Chengalpattu Medical College,. Chengalpattu-603001.

I also certify that this dissertation is the result of the independent work on the part of the candidate.

Prof. Dr.S.PURUSHOTHAMAN MD
Professor and Guide
Department of pharmacology**.**

Prof. Dr. K. BASKAR M.D
Professor & Head of the Department
Department of Pharmacology
Chengalpattu Medical College

Dr.K. MUTHURAJ MS
Dean I/C,
Chengalpattu Medical College

DECLARATION

I solemnly declare that the dissertation entitled **"EFFICACY AND SAFETY OF BROMOCRIPTINE QUICKRELEASE AS AN ADD ON THERAPHY WITH METFORMIN AND GLIPIZIDE IN TYPE 2 DIABETES MELLITUS PATIENTS- AN OPEN LABEL RANDOMIZED CONTROLLED STUDY"** is done by me at Chengalpattu Medical College and hospital, Chengalpattu during the period of 2014 to 2015 under the guidance and supervision of Prof. **Dr. S.PURUSHOTHAMAN, M.D.** This dissertation is submitted to The Tamilnadu Dr.M.G.R. Medical University towards the partial fulfillment of the requirements for the award of **M.D. DEGREE IN PHARMACOLOGY.**

Dr. M. Nithyapriya D.Diab.,
MD Pharmacology Postgraduate Student,
Department of Pharmacology,
Chengalpattu Medical College,
Chengalpattu-603001.

Date: 25.09.2016

Place: Chengalpattu

ACKNOWLEDGEMENT

I express my sincere gratitude to Dean, Prof Dr. **K.MUTHURAJ MS,** Chengalpattu Medical College, for permitting me to undertake this research work as a part of my MD curriculum.

I would like to convey my gratitude to my guide **Prof. Dr. S. PURUSHOTHAMAN M.D**., Professor, Department of Pharmacology, Chengalpattu Medical College for his unfailing guidance, sincere advice and constant support throughout the study.

I would like to convey my gratitude to Prof **Dr. K.BASKAR M.D**., Professor and Head, Department of Pharmacology, Chengalpattu Medical College for permitting me to carry out the study and constant support throughout the study.

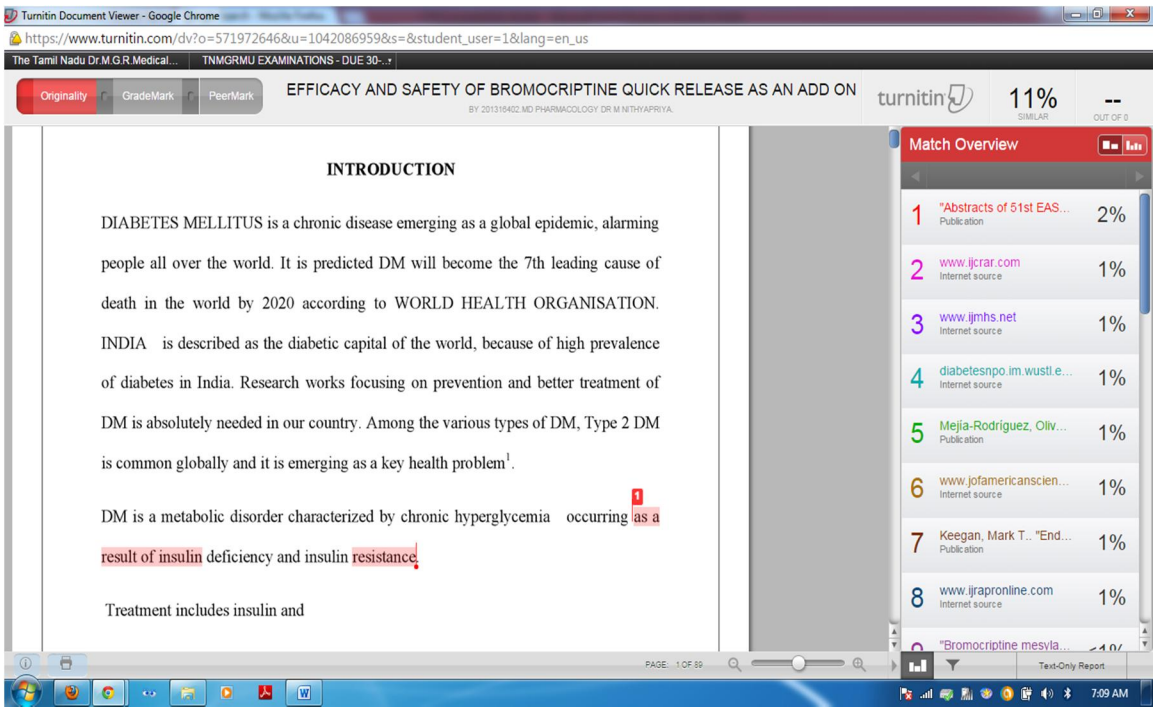
I would like to convey my gratitude to Prof **Dr. SRINIVASAGALU M.D**., Professor and former Head of the Department of General medicine, Chengalpattu Medical College for permitting me to carry out the study in the Diabetic OPD of Chengalpattu Medical College and hospital.

I express my sincere thanks to my Professors, **Dr. R.SIVAGAMI**, **M.D., Dr. B.SHARMILA M.D.,** and Assistant Professors **Dr.T.RAGUPATHY** and **Dr. T SIYAMALADEVI M.D, Dr. B.BHUVENESWARI MD, Dr. R.RANJANI MD, Dr.A.VINOTH MD, Dr.K.RANIDGO, Mr.K.ARUMUGASAMY**, Department of Pharmacology, Chengalpattu Medical College for their advice and encouragement.

I have great pleasure in thanking **Mrs. GLADIUS JENNIFER**, Statistician, for helping me in the statistical analysis. I thank my fellow Postgraduates **Dr.M.NANDHINIPRIYA**, **Dr.SANU SAIN, Dr. S.SWEETLIN**, **Dr. G.AMUDHA** and **Dr. V.J.SHARMI** for their help and encouragement throughout this study.

I wish to place on record my gratitude to my parents and family members for creating a congenial atmosphere and support when it was needed.

Finally I thank all my patients for willingly cooperated and participated in this study.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INTRODUCTION
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DM is a metabolic disorder characterized by chronic hyperglycemia occurring as a result of insulin deficiency and insulin resistance.
Treatment includes insulin and
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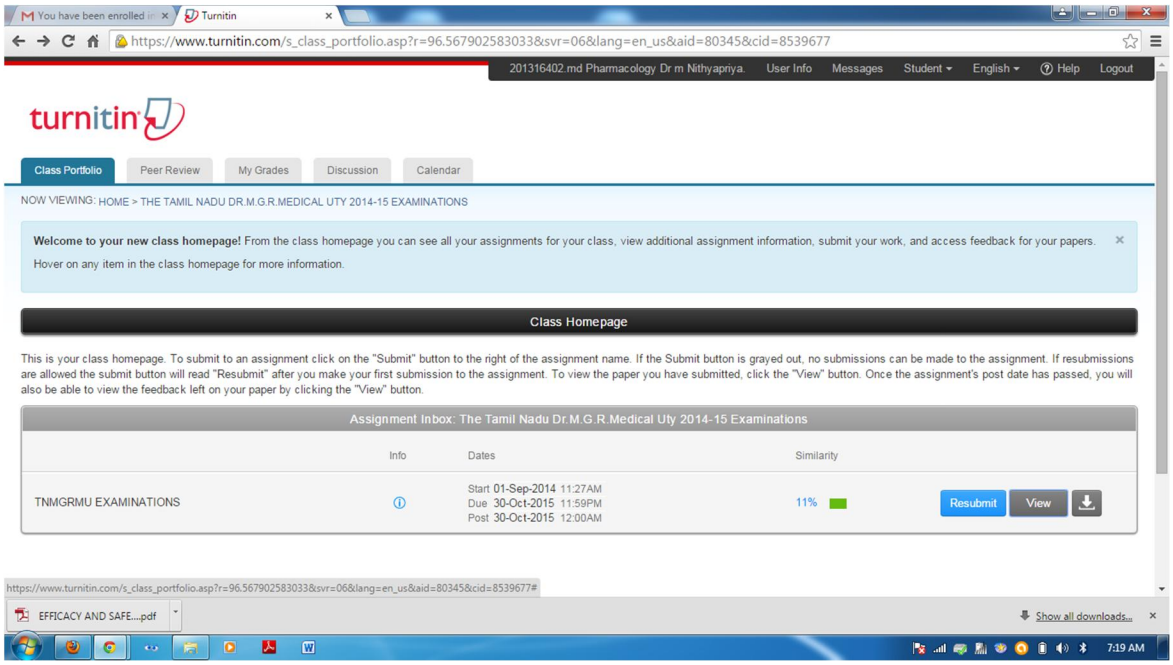
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ABSTRACT

OBJECTIVE

To evaluate the efficacy and safety of bromocriptine Quick release QR as add on therapy with Metformin and glipizide in type 2DM patients.

MATERIAL AND METHODS

140 patients with Type 2 DM satisfying the inclusion criteria were recruited and randomized into two groups. The control group (Group A) was treated with Metformin 500mg bd and Glipizide 5mg bd for a period of 3 months. The study group received Bromocriptine quick release 1.6 mg once daily in the morning in addition to Metformin 500mg bd and Glipizide 5mg bd for a period of 3 months. Fasting blood glucose and postprandial blood glucose were monitored at 0 month, 1st month, 2nd month and 3rd month in both groups. BMI estimation, HbA1C and lipid profile, was done at Baseline and at the end of 3 months in both control and study groups. Baseline investigations to monitor any change in biochemical and hematological parameters were done before and after drug administration in all patients.

RESULTS

There was significant decrease in fasting blood glucose when compared to baseline in both control group [$p<0.05$] taking metformin and Glipizide alone and study group [$p<0.05$] taking Bromocriptine in addition to metformin and glipizide at the end of 3 months.

There was significant decrease in postprandial blood glucose when compared to baseline in both control group [p<0.05] and study group [p<0.05] at the end of 3 months. There was significant decrease in HbA1C when compared to baseline in both control group and study group at the end of 3 months. But the decrease in HbA1C is higher in the study group [p=0.0001] than the control group. [p=0.001].

Also addition of Bromocriptine QR caused significant decrease [P<0.05] of LDL ,TGL and diastolic BP was seen only in study group not in controlgroup. But Total cholesterol, and Systolic BP decreases significantly [p<0.05] in both study and control groups.BMI analysis when compared to baseline did not show any significant decrease in both control and study groups at the end of the study. No serious adverse effects occurred during the study period in both study and control groups.

CONCLUSION

In TYPE 2 DM, Bromocriptine QR when combined with metformin and Glipizide reduced Fasting blood glucose, postprandial blood glucose and HbA1C significantly compared to metformin and glipizide alone.Also, Bromocriptine QR when combined with metformin and Glipizide reduced LDL, TGL, Total cholesterol and blood pressure significantly compared to metformin and glipizide alone.Bromocriptine Quick release is also safe in TYPE 2 Dm at doses of 1.6 mg OD.

KEY WORDS: Bromocriptine, Type 2 Diabetes Mellitus, Metformin, Glipizide.

CONTENT

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ABBREVIATIONS

ADA	-	American diabetes asociation
BMI	-	Body mass index
CKD	-	Chronic kidney disease
CS	–	Continous subcutaneous
CVD	-	Cardiovascular disease
CYP	–	Cytochrome p
D2	–	Dopamine 2
DBP	–	Diastolic blood pressure
DCCT	-	Diabetes control and complications trial
DKA	-	Diabetic ketoaciosis
DM	-	Diabetes mellitus
DPP-4	-	Dipeptidyl peptidase-4
ESRD	-	End stage renal disease
FBS	-	Fasting blood sugar
FFA	-	Free fatty acids
GAD	-	Glutamic acid decorboxylase
GFR	-	Glomerular filteration rate
GLP-1	-	Glucogon like peptide -1
GLUT 4	-	Glucose transporter 4
HDL	-	High density lipoprotein
HHS	–	Hyperglycemic hyperosmolar syndrome
HLA	-	Human leukocyte antigen
HNF	-	Hepatocyte nuclear factor
ICMR	-	Indian council of medical research
IDDM	-	Insulin dependent diabetes mellitus

IDF	-	International diabetes federation
IFG	-	Impaired fasting glucose
IGT	-	Impaired glucose tolerence
IPF-1	–	Insulin promoter factor 1
LDL	-	Low density lipoproteins
LFT	-	Liver function tests
LVD	-	Leftventricular dysfunction
MODY	-	Maturity onset diabetes mellitus of young
NASH	-	Nonalcoholic steatohepatitis
NIDDM	-	Noninsulin dependent diabetes mellitus
NPH	-	Neutral protamine hagedorn
OGTT	-	Oralglucose tolerence test
OHA	-	Oral hypoglycemic drugs
OPD	-	Outpatient department
PAN	-	Peripheral autonomic neuropathy
PCOD	-	Polycystic ovarian disease
PPBS	-	Postprandial blood sugar
PRL	-	Prolactin
PVD	-	Peripheral vascular diseaseqr-quick release
SBP	-	Systolic blood pressure
SD	-	Standard deviation
SGLT 2	-	Sodium glucose cotransporter
SR	-	Sustained release
TGL	-	Triglycerides
VLDL	-	Very low density lipoproteins

INTRODUCTION

DIABETES MELLITUS [DM] is a chronic disease emerging as a global epidemic, alarming people all over the world. It is predicted DM will become the 7th leading cause of death in the world by 2020 according to WORLD HEALTH ORGANISATION. INDIA is described as the diabetic capital of the world, because of high prevalence of diabetes in India. Research works focusing on prevention and better treatment of DM is absolutely needed in our country. Among the various types of DM, Type 2 DM is common globally and it is emerging as a key health problem[1].

DM is a metabolic disorder characterized by chronic hyperglycemia occurring as a result of insulin deficiency and insulin resistance. Treatment includes insulin and Oral hypoglycemic agents [OHA].OHA acts by either increasing insulin secretion or decreasing insulin resistance or both.

Despite the advances in the management of type 2 DM, many patients fail to achieve good glycemic control and suffer from complications of DM. Even with appropriate dosages of OHA and insulin, not all patients are under good glycemic control always. Sulphonylureas can cause weight gain and hypoglycemia as side Effects. Insulin secretogogues can cause exhaustion of pancreas and decrease in insulin secretion on long term treatment [2]. Insulin sensitizers alone are not sufficient for achieving normoglycemia in many patients.

So there is an absolute need for a continuous search of a novel OHA with different mechanism of action and minimal side effects leading to better compliance of patients[3].Restoration of normoglycemia requires OHA with multiple mechanism of action.

Bromocriptine Mesylate QR [Quick release] formulation was approved by FDA in 2009 for treatment of Type 2 DM [4]. It is a unique OHA with central mechanism of action resetting hypothalamic circadian rhythm .Bromocriptine can be utilized in Diabetes Mellitus as monotheraphy and combination therapy[5]. It improves blood glucose by acting through CNS dopaminergic pathways. It addresses the unexplored pathophysiology of DM.

The etiology of diabetes mellitus in India is multifactorial and includes genetic and environmental factors such as obesity, urban migration, and sedentary lifestyle changes.

Because of the heterogeneity of culture, living standards and ethnicity in the Indian population, regional studies and many nationwide multicenter studies are needed. Hence this study was planned to highlight on the usefulness of Bromocriptine QR [quick release] as combination therapy along with metformin and glipizide in Type 2 diabetes. It was an open label randomized controlled study conducted at Chengalpattu Government hospital at Tamilnadu.

REVIEW OF LITERATURE

Diabetes mellitus [DM] is the most common metabolic disorder in the world. Increasing prevalence and incidence of DM and increased complications of DM have created a compelling need to understand the etiopathology and management of DM.

History shows there is a continued advance in understanding the pathophysiology, diagnosis and treatment of Diabetes mellitus [6] .It also gives us a bitter message - despite ever improving treatments, innovative tools, and preventive approaches the conflict to protect diabetic population from its grave problems is difficult.

HISTORY[7]

- 1921- Banting, Best, Macleod, Toronto Demonstrated pancreatic extracts lower blood sugar in experimental dogs
- 1922-Leonord Thompson, Toronto first used insulin in humans.
- 1923-first commercial production of insulin by lily company
- 1955 -Sanger and coworkers illustrated structure of insulin.
- 1942-sulphonylureas discovered.
- 1950-biguanides introduced.
- 1960-Bersin and Yalow made radioimmunoassay of insulin available.

- 1964- Gestational DM Diagnosed by O Sullivan and Mahan.
- 1967-Kelly, Lillie and coworkers made first pancreas transplant.
- 1971-Roth, Cuatrecasus and coworkers defined insulin receptors.
- 1977-Ullrich, Rutter, Goodman and others cloned insulin gene.
- 1981-Kahn and coworkers described insulin receptor kinase activity.
- 1982-Recombinant human insulin came to market.
- 1989-first islet cell transplant.
- 1990-insulin pen devices became available.
- 1995-Metformin became available.
- 2000- Islet transplantation and EDMONTON PROTOCOL was described.
- 2001- [Insulin Glargine, a long acting insulin analogue] introduced by Lantus, Aventis company.
- 2005-GLP1 ANALOGUES available
- 2006- FDA approved DPP4 Inhibitors.
- 2009 –FDA approved use of BROMOCRITINE QR for treatment of Type 2 DM.
- 2013-FDA approved SGLT2 inhibitors.

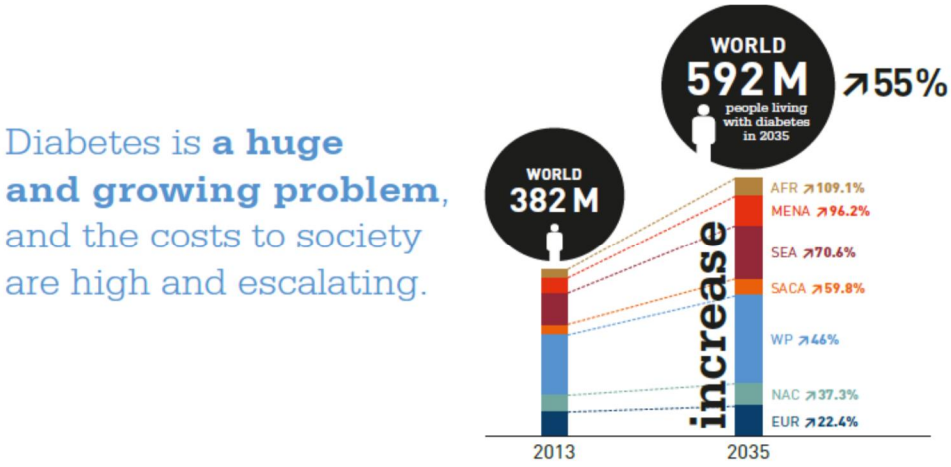
EPIDEMIOLOGY

WORLD

About 285 million people had diabetes worldwide in 2010 of which 90% had type 2 DM[8].Dramatic increase in diabetes was seen in 2013 to about 381 million ,as stated by International Diabetes Federation [IDF]. It is estimated that the prevalence will almost double by the year 2030.The increase in prevalence is expected more in Asian and African countries[9].

About 21 million pregnant mothers are found to be with gestational DM which adds to the universal problem of DM[10.]

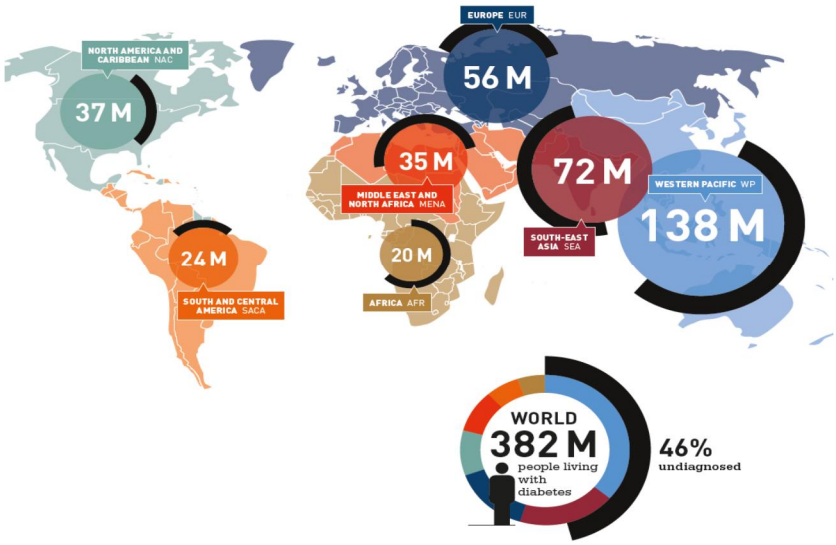
GROWING PROBLEM OF DIABETES MELLITUS



[Adopted from IDF atlas 2014]

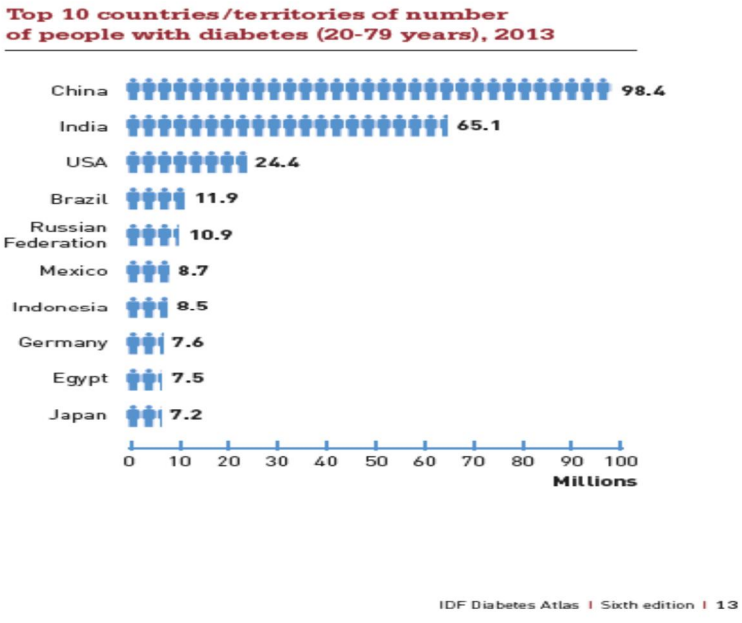
American Diabetes association [ADA] states that By 2030,India will have the highest incidence of Diabetes mellitus [11].

NUMBER OF PEOPLE WITH DM (20-79years), 2013. [Adopted from IDF–SIXTH EDITION/11].



Previously, International Diabetes Foundation stated that India has highest Diabetic population than other nations, but now it is depicted that China has higher diabetic population than us. According to Indian Heart Association, 109 million individuals will be with diabetes by 2035.

TOP 10 COUNTRIES OF PEOPLE WITH DM



India currently faces an uncertain future due to the potential burden imposed by diabetes. Identification of those factors that influences the prevalence of disease throughout our country is necessary to face the health challenges. Genetic susceptibility, unhealthy diet and sedentary lifestyle by the people are mainly the root cause of high incidence of DM.

GENETICS

In type 1 DM, there is a strong genetic association with HLA-B8-DR3 and /or DR4 and recent research shows that when amino acid Aspartate 57 is absent in DQB Gene or when Arginine 52 is present in DQA Gene there is increase susceptibility to TYPE 1 DM[12] .

10% of type 1 DM patients are having parent or sibling with the disease. Studies of monozygotic twins show about 30-50% and dizygotic twins show 5% concordance of developing the TYPE 1 DM. Population studies shows an association between HLA B8 genes DR3-DQ2 and DR4-DQ8[13].

Type 2 DM is a strong genetic disorder. Studies of identical twins reveal 100 % concordance**.** Its inheritance is complex. Several environmental factors particularly central obesity influences Diabetic genotype.

TYPE 2 DM developing below 25 years of age is classified as MODY. [Maturity onset diabetes of young]. It is a noninsulin dependent DM. In MODY, onset of DM is early and it shows autosomal dominant inheritance. Mutations in six discrete genes causes MODY.

The causative genes identified in MODY are HNF4α for (MODY 1)[14] ,Glucokinase for (MODY2),HNF1α for (MODY3)[15],IPF1 for (MODY 4)[16] ,HNF I β for (MODY 5)[17,18] .

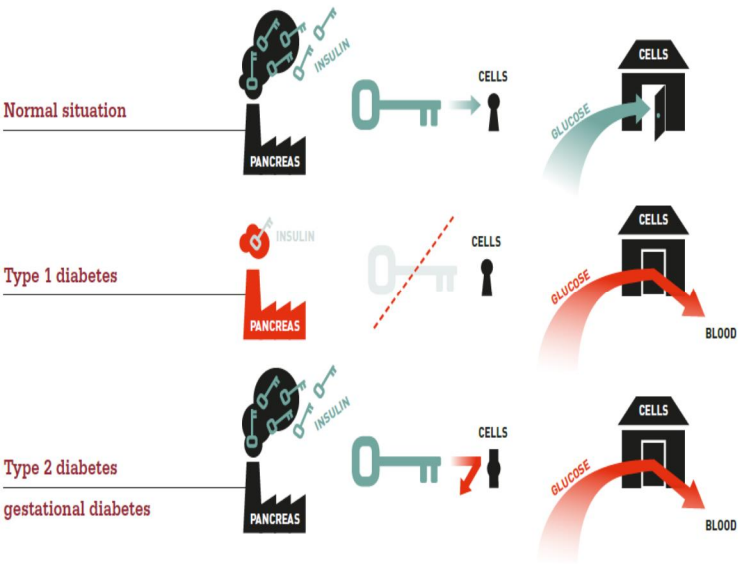
In families with later onset DM , mutations in coding sequence of isle 1 and neuron D1 was found to bepresent.[19] ,[20].Mutations in a single transcription factor gene can impair the expression of many islet genes [21] .

TYPES OF DIABETES MELLITUS:

- Type 1 diabetesmellitus
- Type 2 diabetesmellitus
- Gestational diabetes mellitus
- Other forms of diabetes.
  - Genetic faults of beta cell dysfunction e.g., MODY 1 to 6
  - Genetic faults in insulin action.
  - Ailments of Exocrine pancreas, e.g., Fibro calculus pancreatopathy

    Diseases of Endocrine system e.g., Acromegaly, Cushing's, etc.
  - Drugs induced, e.g., glucocorticoids
  - Infections such as congenital rubella
  - Rarely immune mediated diabetes ,such as Stiff Man Syndrome
  - Other Genetic syndromes

TYPES OF DIABETES



Adopted from IDF atlas sixth edition / page no: 12.

The American Diabetes Associations [ADA] new classification for diabetes is etiologically based, not based on the type of treatment. Type 1 DM and Type 2 DM is the preferred nomenclature instead of IDDM and NIDDM. Less common types of diabetes include Gestational Diabetes Mellitus and Prediabetes.

TYPE 1 DIABETES MELLITUS

Type 1 Diabetes also called as IDDM is caused by beta-cell damage, and absolute insulin insufficiency. Exogenous insulin doses are needed for survival of TYPE 1 DM. Patients, on withdrawal of insulin develops hyperglycemia, DKA, coma. Onset of age-usually childhood and adolescence, peak at 5 &15 years[22] .5- 10% of persons get type 1 DM above 30 years of age[23] .The etiology of TI DM is beta cell destruction and absolute insulin deficiency. Based on this it is further divided in to 2 types

- Type 1a: Autoimmune [islet cell antibody and GAD positive].
- Type 1b: Idiopathic
- Autoimmune destruction is triggered either due to viral infection such as congenital rubella ,coxsackie virus,mumps,reo virus ,herpes virus, echo viruses. or due to environmental factors such as

- Increased ingestion of certain medications that may compromise pancreas:

    - Anticancer drugs such as Streptozotocin, Hexamethylmelamine and antihistamine such as Cyproheptadine, and rodenticide such as vacor.

- Increased free radicals due to changes in environment that damage DNA in insulin producing cells.

ETIOPATHOGENESIS OF TI DM

Genetic susceptibility
↓
Environmental factors
↓
Immunological activation
↓
Progressive β cell destruction
↓
Type 1 Dm

DIAGNOSIS OF TYPE 1 DM

If estimation of glucagon stimulated C-PEPTIDE LEVELS show absence or very low levels of C-PEPTIDE, it is diagnostic of TYPE 1 DM. These patients have very low β cell reserve.

TYPE 2 DIABETES MELLITUS

Among the diabetic population 95% are of type 2 DM and only 5% suffer from type 1 DM. Usual age of onset is >30 years. But recently obesity and occurrence of Type 2 DM in adolescent and childhood age is becoming more common.[24].

Family history is the main risk factor for type 2 diabetes. Progressive decrease in secretion of insulin from pancreas and increase in insulin resistance leads to type 2 DM.[25.]

Exogenous insulin is usually needed only at times of stress for glycemic control. Insulin Resistance and obesity plays a key role in Type 2 DM. Liver, skeletal muscle and adipose tissue mainly shows insulin resistance.

Possible causes of INSULIN RESISTACE type 2 Diabetes

- Decreased insulin receptors on target cells
- Decreased efficacy of insulin receptors
- Defect in the post-receptor events.
- Genetic component

OTHER WARNING FACTORS FOR TYPE 2 DIABETES

Family history, Increasing age, central obesity, and sedentary lifestyle.

ETIOPATHOLOGY OF TYPE2 DM:

Genes , Obesity, B Cell Capacity, Insulin Resistance

↓

Environment, Abundant Food, Less Physical Activity

↓

Insulin Resistance, Hyperinsulinemia [βcellcompensation]

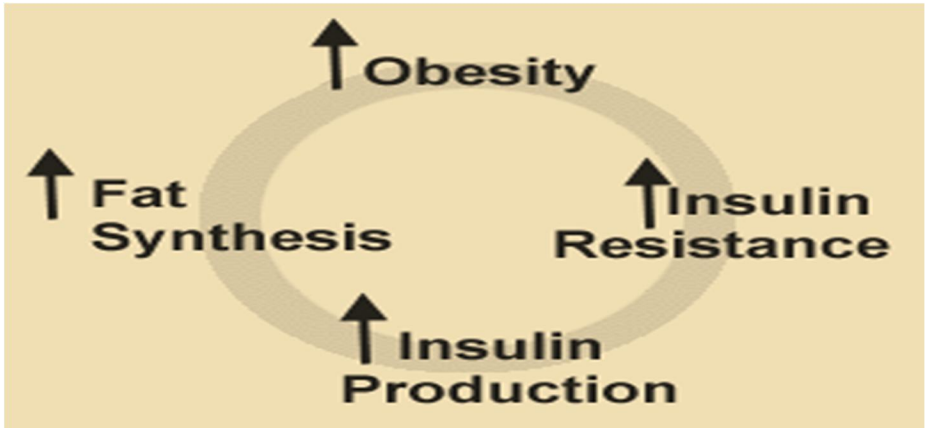
↓

B Cell Decompensation, IGT

↓

Declineof β cellmass,Severe Hyperglycemia, Hypoinsulinemia, Glucotoxity,Type 2dm

OBESITY AND TYPE2 DIABETES MELLITUS



One of the important risk factor for type 2 DM is obesity. Obesity aggravates type 2 diabetes.

As body fat increases, insulin resistance increases due to decrease in insulin receptor number and decline in receptor function. Type 2 diabetes and obesity becomes a viscous cycle. Therefore obese individuals need extra insulin than non-obese individuals to preserve normal blood glucose.

CLINICAL SYMPTOMS OF TYPE 2 DIABETESMELLITUS:

Type 2 diabetes usually present with less dramatic symptoms than that of type 1.Many type 2 diabetics are undiagnosed. They come with nonspecific symptoms of their complication and identified with hyperglycemia. Symptoms of Type 2 Diabetes are

- polyuria, polydipsia ,polyphagia
- Blurred vision
- Pruritus vulvae
- Skin infections

GESTATIONAL DIABETESMELLITUS

When glucose intolerance develops or when it is recognized in pregnancy it is defined as gestational diabetes mellitus. It usually reverts back to normal in the postpartum period. In future they have increased risk of evolving into Type 2 DM. Periodic monitoring thereafter is needed for them.

Screening for and diagnosis of GDM

Diagnosis of GDM is by glucose tolerance test .OGTT to be done at 24-28 weeks of pregnancy. After parturition, OGTT is to be done after 6 weeks, after 6 months and then yearly checkups needed.

DIAGNOSIS OF DM

Diagnostic characteristic for diabetes mellitus is hyperglycemia. Stress and medications can cause hyperglycemia as a side effect. Hence proper diagnoses of DM are essential.

ADA CRITERIA FOR THE DIAGNOSIS OF DIABETES[26]

- A1C >6.5%.
- FASTING PLASMA GLUCOSE > 126 mg/dL or (7.0 mmol/L). *
- POSTPRANDIALPLASMA GLUCOSE >200mg/dL or (11.1mmol/L)
- **OR**
- Hyperglycemic symptoms/ crisis with a Random Plasma Glucose>200 mg/dL or (11.1 mmol/L)

Rationale for the diagnostic criteria:

- FBG and 2-h BG levels are proportional to risk of micro vascular and macro vascular disease.
- FBG is simpler and cheaper test than OGTT.

CARPENTER AND COUSTAN CRITERIA FOR DIAGNOSIS OF GESTATIONAL DIABETES MELLITUS

100g OGTT

- Fasting: >95 mg/dl (5.3 mmol/L)
- 1 h: >180 mg/dL (10.0 mmol/L)
- 2 h: >155 mg/dL (8.6 mmol/L)
- 3 h:>140 mg/dl(7.8 mmol/l)

75 g OGTT

- Fasting: >95 mg/dl (5.3 mmol/L)
- 1 h: >180 mg/dL (10.0 mmol/L)
- 2 h: >155 mg/dL (8.6 mmol/L)

PREDIABETES:

- A1C 5.7–6.4%
- FPG 100 TO 125 mg/dl is said to be impaired fasting glucose;
- PPBG 140 TO 199mg/dl is said to be impaired glucose tolerance**.**

COMPLICATIONS OF DM:

The metabolic derangement in DM leads to secondary pathophysiologic changes affecting multiple organs and imposes a problem not only on the individual with diabetes but also on the health care system[27.]

Complications of DM can be acute or chronic.

Acute Complication

Results from acute changes in blood glucose.

- Diabetic ketoacidocis,
- Hyperglycemic hyperosmolar syndrome (hhs),
- hypoglycemia.

Chronic (long-term) complications:

Microvascular complications

- Retinopathy (nonproliferative/proliferative)
- Neuropathy
- Peripheral neuropathy/
- Autonomic neuropathy
- Nephropathy

Macrovascular Complications:

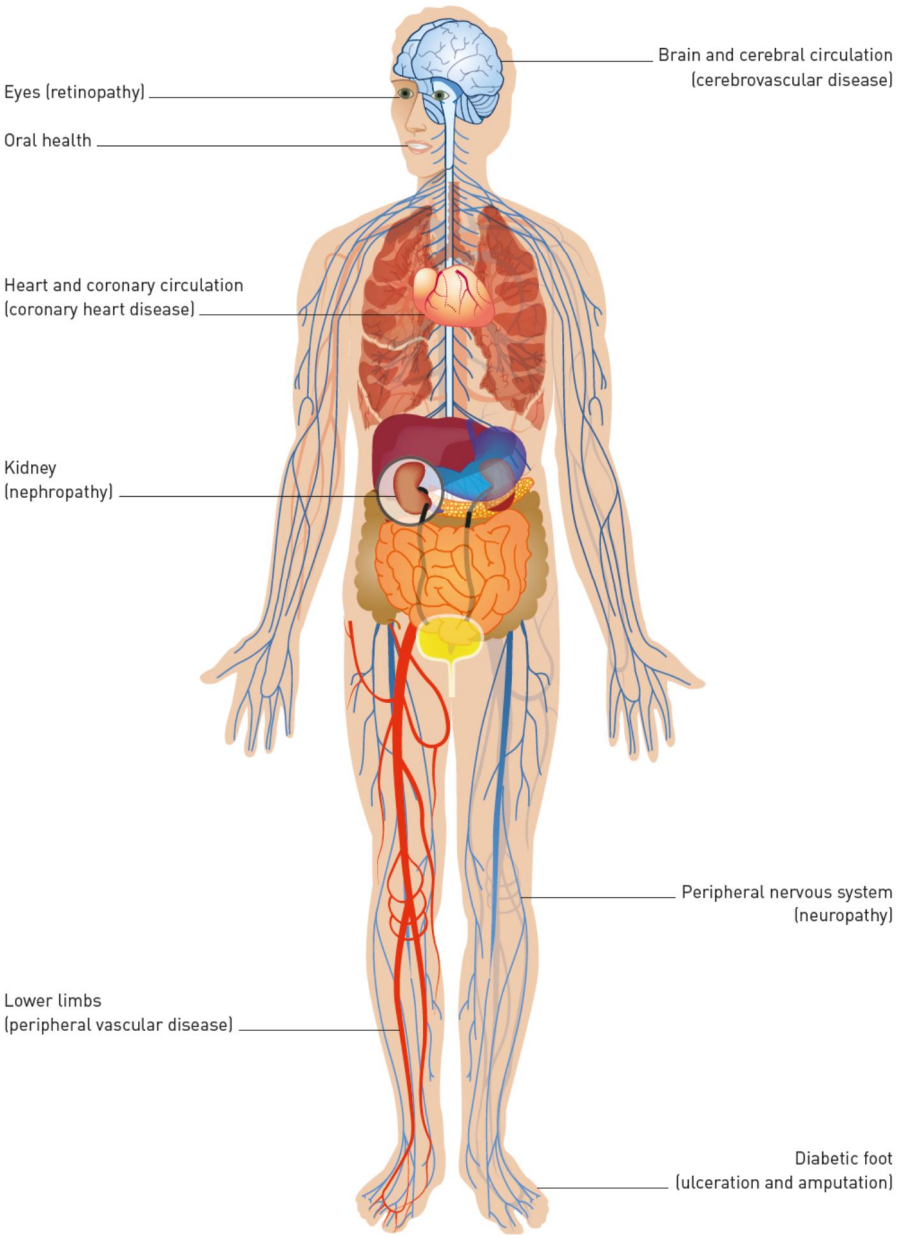
- Coronary artery disease
- Cerebrovascular disease
- Peripheral vascular disease

Additional complications

- (Gastro paresis, loose stools)
- (uropathy/erectile dysfunction)
- Skin diseases
- Infections

- Cataracts
- Glaucoma
- Periodontal disease
- Hearing defects

MAJOR COMPLICATIONS OF DIABETES MELLITUS

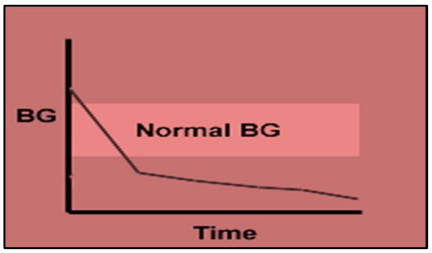


ACUTE COMPLICATIONS

Hypoglycemia

It is the most frequent and dangerous acute complication usually resulting from insulin therapy28, 29. Inappropriate timing of food, exercise, and insulin treatment can lead to hypoglycemia30.

HYPOGLYCEMIA



Symptoms of hypoglycemia include:

- Symptoms of sympathetic activation:

Pallor, tremor, palpitations, anxiety, hunger, vomiting, fever, moderate tachycardia, systolic hypertension.

- Symptoms of parasympathetic activation:

Nausea, eructation, sweating, bradycardia, hypotension.

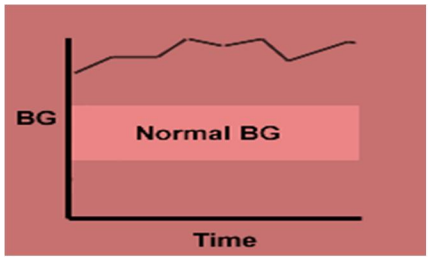
- Signs and symptoms of neuroglycopenia:

Headache, dizziness, fatigue, irritability, perioral numbness, disturbed vision, paresthesia, confusion, cognitive impairment, psychotic behavior, Occasionally focal neurological defects, hemiparesis, convulsions, coma death. Hypoglycemic unawareness is mostly seen in chronic diabetes. It warns for regular and periodic monitoring of blood glucose in them.

HYPERGLYCEMIA

High blood glucose by osmosis causes intracellular and extracellular fluid depletion and dehydration. It also results in excessive urination and thus dehydration.

HYPERGLYCEMIA



Symptoms of hyperglycemia include:

- Polydipsia and polyuria
- increased hunger
- loss of Weight
- Unclear vision.
- breath smells of acetone (due to ketosis)
- Glycosuria
- Labored breathing
- Coma (from ketoacidosis commonly seen in type 1 diabetics)
- Hyperosmolar hyperglycemic non ketotic coma (in type 2 diabetics)
- Death

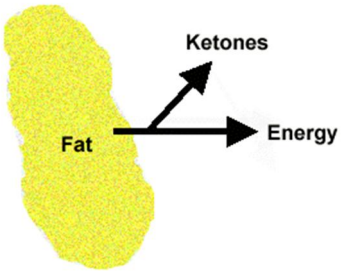
Amplified mortality in DM is produced by DKA and HHS.

DIABETIC KETOACIDOSIS

Type 1 DM usually exhibits DKA as its common complication .But at times of catabolic stress, Type 2DM also presents with DKA[31.] Hyperglycemia and increased circulating total body ketone levels causes metabolic acidosis. When there is shortage of insulin and simultaneous raise of counter regulatory hormones ketoacidosis occurs[32,33.] This hormonal imbalance leads to increased

lipolysis and ketosis .Ultimately this acidic ketones lead to DKA and its manifestations.

LIPOLYSIS AND KETOSIS.



CRITERIA FOR DIAGNOSIS OF DKA:

Blood glucose level more than 250 mg/dl, presence of ketonemia or ketonuria, serum bicarbonate lessthan15 me/l, pH less than 7.3 in ABG, [metabolic acidosis] [34.]

Treatment of DKA includes fluid therapy, insulin therapy, potassium, and bicarbonate and phosphate correction[34.]

HYPERGLYCEMIC HYPEROSMOLAR SYNDROME (HHS):

HHS is common in type 2 diabetes. About 7–17% of diabetic patients manifest HHS as their first manifestation of DM[35.] The major precipitating factors are infections, especially UTI and pneumonia, cerebrovascular disease or myocardial infarction.[35] Treatment of HHS in general includes systematic monitoring of blood glucose, rectification of hypervolemia and electrolyte losses, and treatment of precipitating causes in addition to insulin therapy.

CHRONIC COMPLICATIONS:

Retinopathy, neuropathy and nephropathy are the chronic complications of DM. The UKPDS Study demonstrated that, in type 2 DM decrease in mean HbA1C, seen in intensive therapy [7.9%] is more when compared to conventional therapy [7.0%] [36.] It also states that overall 25% decrease in rate of micro vascular complications is caused by intensive treatment in type 2 DM[36]

END STAGE RENAL DISEASE is commonly due to DM. About 40% of Type 1 diabetic patients suffer from severe kidney disease above 50 years of age.

NEPHROPATHY

Diabetes is the most common cause of ESRD, resulting in about one-third of new ESRD patients every year. Nearly 40% of people with type 1 diabetes develop severe kidney disease and ESRD by the age of 50.

KIDNEY DAMAGED BY DIABETES

The kidney disease progresses to ESRD in about 17 years in Type 1 DM. Hypertension and atherosclerosis affects kidney vessels and contribute to nephropathy. Micro proteinuria is an initial manifestation of kidney damage. Progression of nephropathy can be slowed by Angiotensin-converting enzyme (ACE) inhibitors and Calcium channel blockers .Low protein diet are also found to be useful. Intensive treatment of hyperglycemia caused a 50% reduction in both incidence and progression of nephropathy according to the DCCT.

RETINOPATHY

Poor glycemic control increases the risk of retinopathy. Several studies identify hyperglycemia, high blood pressure and hypercholesterolemia as risk factors for Diabetic retinopathy[37, 38.39,40,41.].. Decrease of HbA1c to 7%, decreased development and advancement of Diabetic Retinopathy in diabetes mellitus patients [42, 43, 44.]

The DCCT study also detected that intensive treatment of DM minimized the risk of retinopathy by 76%.Intensive control of blood glucose in early stages of diabetic retinopathy decelerated the progression of eye damage by 50%.

DIABETIC NEUROPATHY

Hyperglycemia is highly linked with the occurrence and progression of all neuropathies, comprising Peripheral diabetic neuropathy [PDN].[45, 46.] The Diabetes Control and Complications Trial (DCCT) established that the incidence of neuropathy will be decreased by 60% as the result of tight

glycemic control[47]. *But the incidence of neuropathy remains 20%, even after good glycemic control*[48]. Significant nerve damage can be decreased by 60% if blood glucose is strictly controlled as stated by DCCT.

Types of neuropathy include

- Peripheral neuropathy
- Mononeuropathy
- Autonomic neuropathy

CARDIOVASCULAR DISEASE AND STROKE

Diabetic Patients are under high risk of succumbing to cardiovascular disease (CVD) and stroke. The increased morbidity and mortality in diabetes patients is mainly attributed to CVD[49]. Congestive cardiac failure is increasingly seen in DM.

Hyperglycemia leads to glycosylation of proteins including LDL Apo proteins. Hyperinsulinemia has also been implicated as cause of atherosclerosis leading to CVD and stroke. Elevated cholesterol values are seen more in Diabetics than Nondiabetics[50, 51]. Other risk factors of type 2 DM are commonly present, such as hypertension, obesity, lack of exercise, age, and smoking.

MANAGEMENT OF DIABETES MELLITUS

Diabetes management is an ongoing and continuous process. To ensure the best possible outcomes, it should involve diet, exercise, medication, and monitoring.

The American Dietetic Association recommends medical nutrition therapy for diabetic patients as follows

- Maintain a balance between food /insulin / oral glucose lowering medications and exercise levels.
- Maintain normal serum lipid levels
- Provision of adequate calories for maintaining normal weights for adults, normal growth in children and adolescents, and for meeting the metabolic needs of pregnancy ,lactation, and catabolic illnesses
- Prevention and management of the complications of DM.

The cornerstone in diabetic management is diet and exercise. The dietary management should be aimed at and achieving maintaining ideal body weight, normal lipid profile and euglycemia.Diet should be individualized considering ethnic, cultural issues and comorbid conditions.

TOTAL CALORIES DISTRIBUTION

[ICMR Guidelines –nonpharmological management of DM]

Carbohydrates **should be 55-60% of total requirement**:

The main source should be cereals, pulses, grains, soyabeans.It is advised that roots and tubers to be used sparingly. Use of honey, sugar, sweeteners and Maida products to be avoided.

Proteins should be 10-15% of total requirement.

It should be from vegetables, fish, lean meat and low fat milk and milk products.

Fat should be 20-25% of total requirement

Less than 7% should be saturated fat; the remaining should be MUFA and PUFA. Dietary cholesterol should not exceed 300mg/day. Ricebran oil,groundnut oil ,sesame oil have linoleic acid n-6 and oil containing α linoleic acid such as mustard oil,soyabean etc to be used. Diet rich in fruits and fiber to be advised.common salt intake less than 6g% to be advised. Alcohol aggrevates obesity,dyslipidemia and neuropathy.so it should be avoided,or to be taken only moderately.use of tobaco and smoking to be prohibited.

Exercise/ Activity

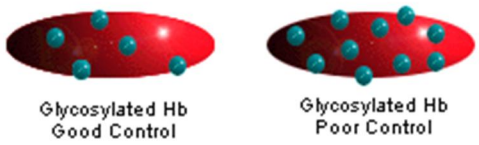
Effect of exercise revealed beneficial results for T2DM deprived of any adverse effects. The benefits of exercise such as reduction of bodyweight are of greater utility in obese patients with diabetes mellitus[52, 53.]

In the skeletal muscle increased glucose uptake via glucose transporter 4 (GLUT4) during the exercise causes decrease in the blood sugar level in T2DM patients [54]. 30 to 45 min of aerobic exercise, 3 to 5 days in a week (minimum of 150 min/week) is advisable. Walking 1 hour/day or jogging 30 min/day will lead to decrease in body weight on longterm.[55.]

MONITORING OF DIABETIC PATIENTS:

Glycemic control over the past 2-4 months can be picked up by Glycosylated hemoglobin, (HbA1c). Normal range of DM is 4-6%

Glycosylated Haemoglobin



- Periodic Ophthalmic evaluation and renal and cardiac status evaluation is essential.

DRUG THERAPY TO DM

1. Insulin Therapy
2. Oral antidiabetic medications

INSULIN THERAPY.

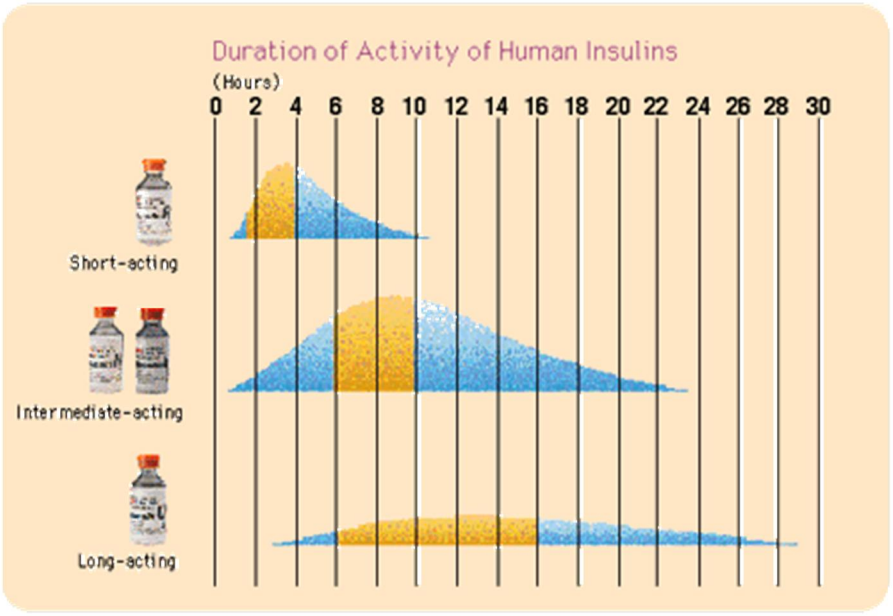
Type 1 diabetics need insulin therapy for survival, and many type 2 diabetics need insulin therapy for glycemic control .Source of exogenous insulin is used and human insulin has been available since 1980. Insulin used now days is prepared by recombinant DNA technology. There are 3 types of insulin based on their duration of action as shown below.

PROPERTIES OF INSULIN INJECTIONS

Properties of Insulin Injections	**Action time-hours**		
Preparation	**Onset,**	**Peak,**	**Duration,**
Short-acting			
As part	<0.25	0.5–1.5	3–4
Glulisine	<0.25	0.5–1.5	3–4
Lispro	<0.25	0.5–1.5	3–4
Regular	0.5–1.0	2–3	4–6
Long-acting			
Detemir	1–4	—[a]	24
Glargine	1–4	—[a]	24
NPH	1–4	6–10	10–16
Combinations of Insulin			
[75/25] 75% protamine Lispro, 25% Lispro	<0.25	1.5 h	10–16
[70/30]70% protamine Aspart, 30% as Aspart	<0.25	1.5 h	10–16
[50/50] 50% protamine Lispro, 50% Lispro	<0.25	1.5 h	10–16
[70/30] 70% NPH, 30% regular	0.5–1	Dual	10–16

Adopted from Harrison’s textbook of medicine

DURATION OF ACTION OF HUMAN INSULIN



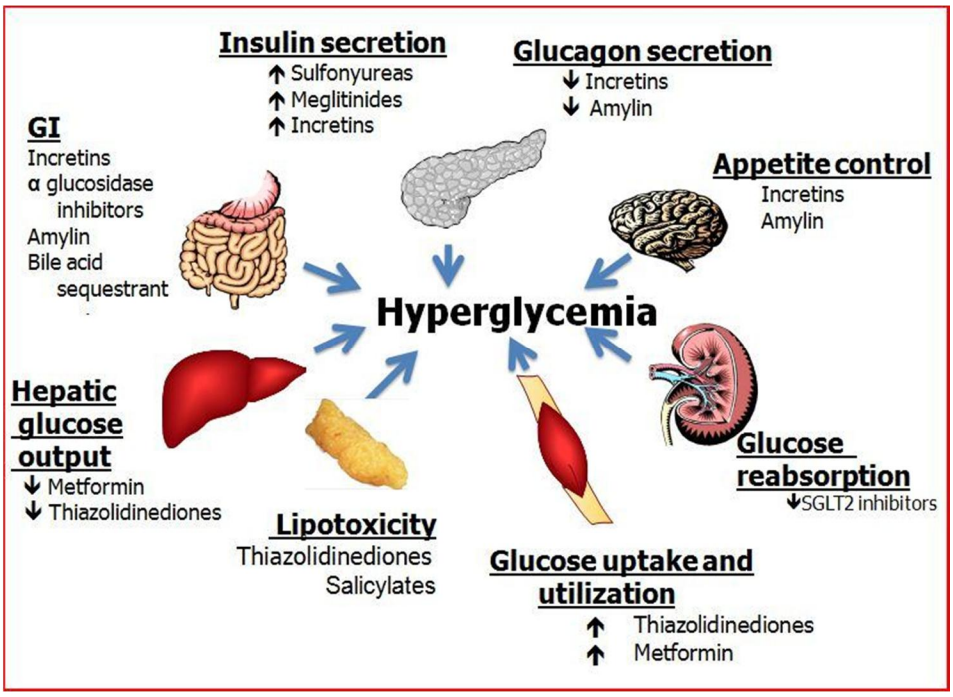
Insulin injection regimen should mimic the body's physiological insulin pattern as much as possible. Rapid acting insulin controls of meal surges; long acting mimics the baseline secretion. Ultra-rapid acting insulin can be injected just prior to ingesting an unplanned food.. Insulin is injected 2-3 times a day, as a mixture of long and intermediate or rapid acting insulins. Usual dosage of insulin is 0.5 to 1 unit of insulin per kg body weight insulin dosage needs to be decreased with exercise and increased with stress (pregnancy, surgery, illness).

Insulin pumps are used by some diabetics allows greater flexibility in diet and tight control of blood glucose. The continuous subcutaneous insulin infusion (CSII) system consists of a preprogrammed pump. It provides insulin at a basal quantity between meals and more bolus of insulin at meal times.

ANTIDIABETIC DRUGS

- ORAL HYPOGLYCEMIC DRUGS
- Sulphonylureas; Meglitinides.
- ANTIHYPERGLYCEMIC AGENTS
- Metformin,
- Thiazolidinediones
- A Glucosidase Inhibitors,
- DPP 4 inhibitors,
- Incretin Mimetics,
- Amylin receptor agonists.

PRIMARY ACTIONS OF ANTIDIABETIC DRUGS



1. **SULPHONYLUREAS**

Mechanism of action: it increases insulin secretion.

HbA1c reduction: 1-2%

Advantages: inexpensive

Adverse effects: weight gain and hypoglycemia

Contraindications: kidney and liver disease.

2. **MEGLITINIDE ANALOGUES**:

Mechanism of action: it increases insulin secretion.

Advantages: Quick and short acting. Decreases PPBS.Nateglinide can be used in patients with liver dysfunction.

Adverse effects: hypoglycemia. [If meal is skipped]

Contraindications: liver diseases.

3. **BIGUANIDES: METFORMIN**

Mechanism of action: it decreases hepatic output of glucose.

HbA1c reduction: 1-2% reduction is seen with metformin.

Advantages: it is weight neutral, it does not cause hypoglycemia.

Adverse effects: nausea, diarrhea and other GI side effects, lactic acidosis rarely.

4 . **THIAZOLEDINEDIONES:**

Pioglitazone

Mechanism of action: decreases insulin resistance by PPAR – γ agonistic action.

HbA1c reduction: 0.5-1.4%

Advantages: it decreases insulin resistance and increases peripheral glucose uptake.

Adverse effects: peripheral edema, CHF, weight gain, fractures, macular edema.

Contraindications: CHF, liver disease.

Rosiglitazone has been withdrawn from market because it causes increased CVS risk.

5. **BILEACID SEQUESTRANTS**:

COLESEVALAM

Mechanism of action:

It binds bile acids and it decreases blood glucose by unknown mechanism

HbA1c reduction: 0.5% reduction is seen.

Adverse effects: constipation, dyspepsia, abdominal pain, nausea, intestinal obstruction.it also interferes with absorption of other drugs.

Contraindications: elevated plasma triglycerides.

6. **GLUCOSIDASE INHIBITORS**

Acarbose, miglitol.

Mechanism of action: it decreases intestinal glucose absorption

HbA1c reduction: 0.5-0.8%

Advantages: Decreases PPBS

Adverse effects: gastrointestinal adverse effects, flatulence, abnormal liver function tests.

Contraindications: kidney and liver disease

7. **DPP 4 Inhibitors**

Saxagliptin, sitagliptin, vildagliptin.

Mechanism of action: it prolongs endogenous GLP 1 action which stimulates insulin secretion.

HbA1c reduction: 0.5-0.8%

Advantages: hypoglycemia does not occur.

Contraindications: renal disease needs reduction of dose.

8. **GLP 1 RECEPTOR AGONISTS**

Eventide, liraglutide.

Mechanism of action: it increases insulin secretion, decreases glucagon secretion, slows gastric emptying, satiety.

HbA1c reduction: 0.5-0.1%

Advantages: causes weight loss, do not cause hypoglycemia.

Adverse effects: given as SC injection; hypoglycemia when given with insulin secretogogues, pancreatitis, Kidney failure.

Contraindications:

Renal disorder, drugs that decrease GI motility.

DESCRIPTION OF DRUGS USED IN STUDY

- Metformin
- Glipizide
- Bromocriptine

METFORMIN

- It is an insulin sensitizer belonging to biguanides group.it has direct anti-hyperglycemic action.
- It is the first line drug in obese type 2 DM.

MECHANISM OF ACTION

It reduces hepatic glucose output and it augments glucose utilization by muscles .It also decreases FFA availability by inhibiting lipolysis.

At cellular level, it increases insulin sensitivity

- By increasing insulin binding,
- Stimulating insulin receptor tyrosinase kinase activity
- Enhanced glucose transport [GLUT 4]

- Increases glycogen synthase.
- In addition, it also has anorexogenic effect, and it also inhibits intestinal absorption of glucose.
- Advantage over sulphonylureas:
- It is only antihyperglycemicagent but not hypoglycemic agent
- DOSAGE: available as 250 mg, 500mg, and 850mg tablet 500mg and 1 g SR tablets also available.

THERAPEUTIC USES

- Obese type 2dm,
- Secondary failure to sulphonylureas
- Brittle diabetes
- In insulin resistance to decrease insulin requirements
- PCOD
- Non Alcohic Steatohepatitis [NASH].

SIDE EFFECTS

- ❖ Gastrointestinal Effects -20% experience anorexia, nausea, vomiting and diarrhea, B12 malabsorption in 2000mg or more.
- ❖ Lactic Acidosis

Contraindications

- Impaired renal function [serum creatinine ≥ 1.5mg/dl in man, ≥ 1.4mg/dl I women; GFR <70 ml/min.]
- symptomatic CHF requiring pharmacologic treatment
- chronic liver disease
- elderly
- pregnancy
- lactation
- type 1 DM
- patients with alcohol dependence

GLIPIZIDE

Is an insulin secretogogues, belonging to second generation sulphonylureas.

Mechanism of action

Competitively blocks the sulphonyl urea receptors on the beta cells of pancreas

ATP sensitive K channels is blocked

↓

Depolarization

↓

CA $^{2+}$ entry

↓

Insulin secretion.

It lowers postprandial blood glucose by causing increased insulin release. It also has extra pancreatic effect of increased insulin sensitivity by increase in receptor numbers and post receptor effect[56].

PHARMACOKINETICS

Dosage-2.5-40 mg/day

Duration of action of effect: 12-24hours; halflife 1-4 hours; available as 5mg tablet Can be given OD or BD. Glipizide is absorbed rapidly and has short duration of action.

ADVERSE EFFECTS

Gastrointestinal side effects [nausea, vomiting, heartburn, hepatitis and cholestasis] skin rashes, blood dyscrasias common to all sulphonyl ureas

Contraindications

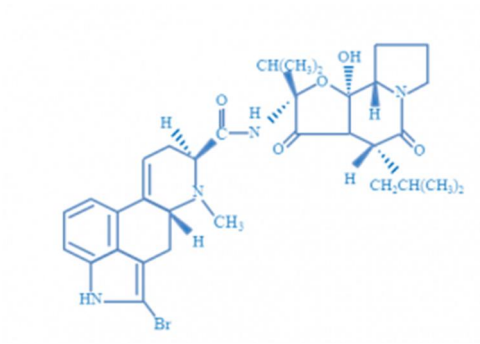
- Type 1 DM
- Pregnancy
- Allergy To Sulphonyl Ureas
- Liver And Kidney failure
- Surgery And Postoperative period
- Severe Infections

BROMOCRIPTINE

Bromocriptine is a dopamine D2 receptor agonist acting centrally. . It has a strong agonistic action on dopamine D2-receptor .It inhibits pituitary secretion of PRL[prolactin]. Bromocriptine also possesses partial D1-receptor

agonist activity, 5-HT2 antagonist effects and mild adrenergic effects.[57.] Chemistry: it is a tetracyclic ergo line compound derived from plant alkaloids.

MOLECULAR STRUCTURE OF BROMOCRIPTINE QUICK RELEASE.



Pharmacokinetics

Dosages: Bromocriptine quick release is administered once daily and within 2 hours of awakening. The recommended initial dose is 0.8 mg daily, increased by 0.8 mg weekly (1.6 - 4.8 mg). It is to be managed as a only daily dose within two hours of awakening in the morning and preferably with diet to minimize nausea... When administered orally, about 65-95% is absorbed within 30 minutes.

The peak plasma concentration is reached in about 53-60 minutes if the patient is on an empty stomach... The absorption is delayed by the food. Due to an extensive first-pass effect in the liver bioavailability is only 7 %.

In other indications 5.0–7.5 mg/day causes marked fall in the concentration of circulating prolactin. Higher doses are needed to treat acromegaly and Parkinsonism. Bromocriptine is metabolized in liver by cytochrome P 450[CYP3A4], and approximately 16-30 metabolites are

formed. The biologic activity of these metabolites is not known. The main route of excretion is biliary route; 2-6% is excreted via the kidneys approximately. Common side effects include nausea, headache, vomiting dizziness and fatigue[58.]. These side effects occur mainly during the initial titration phase and are transient, lasting around 14 days.

It can cause syncope and orthostatic hypotension in patients taking antihypertensive patients. [Especially on initiation and dose escalation]. Bromocriptine inhibits lactation in nursing women.

CONTRANDICATIONS:

- Type1 DM
- Syncopal attacks
- psychosis
- hypersensitivity to ergot-related drugs/Bromocriptine

DRUG INTERACTIONS

- ❖ since Bromocriptine is chiefly metabolized by CYPA4 enzyme pathway,
- ❖ CYPA4 inducers decrease the plasma level of Bromocriptine and CYP3A4 inhibitors increases the plasma concentration of Bromocriptine.
- ❖ Bromocriptine Mesylate –highly protein bound; can displace other protein bound drugs such that salicylates, sulfonamides, chloramphenicol, probenacid and so alter their action.

- ❖ Dopaminereceptorantagonists:-antipsychotics [phenothiazine, thioxanthenes butyrophenones] and metoclopramide decrease the efficacy of Bromocriptine and vice versa.

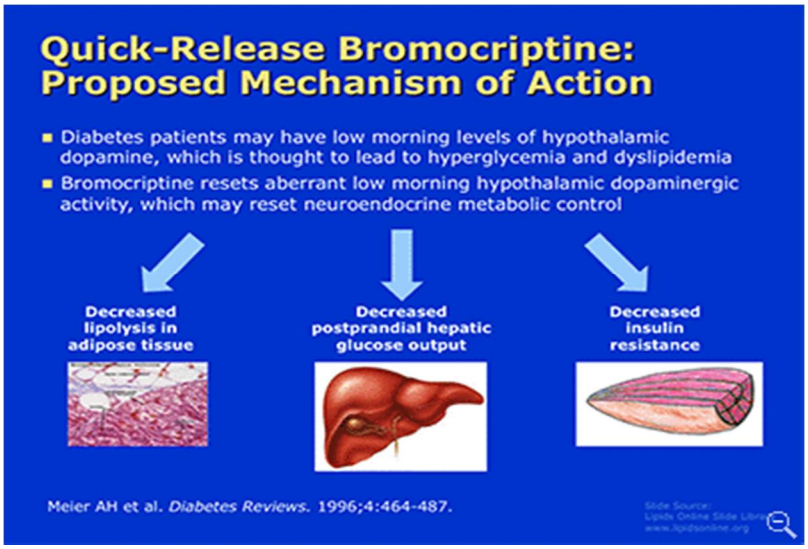
- ❖ When used with ergot associated drugs, it increases side effects of ergot drugs, so not to use ergot agents within six hours of Bromocriptine intake.

MECHANISM OF ACTION OF BROMOCRIPTINE

It has a unique mechanism of action that decreases plasma glucose, triglycerides, FFA levels, and thus decreases cardiovascular risk. The benefit of Bromocriptine in diabetes mellitus is through modulating central glucose and energy metabolism pathways[59, 60.]

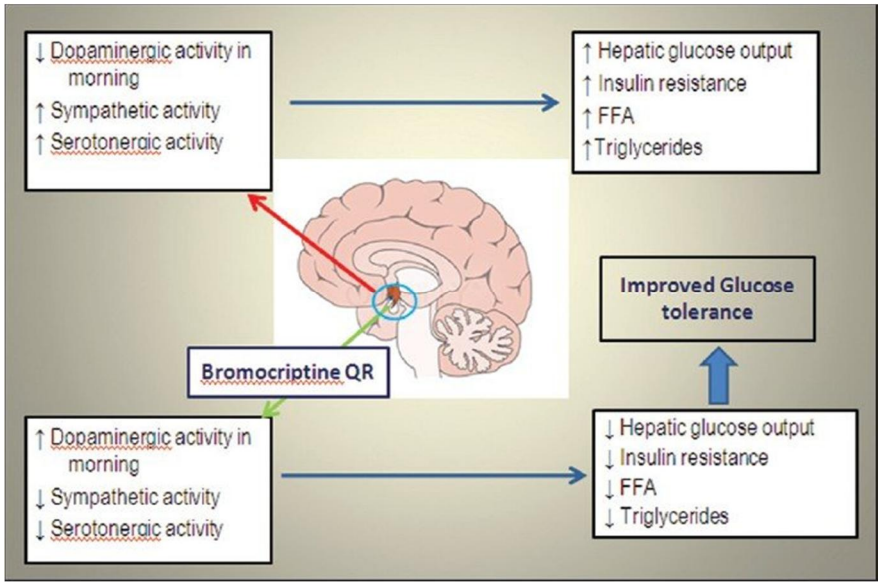
It can be used as monotheraphy or as combination therapy to antidiabetic medications like metformin/sulfonylurea. It is not recommended for the treatment of type-1 diabetes or diabetic ketoacidosis. Bromocriptine is administered within two hours of awakening as a quick release formulation. It augments the hypothalamic dopamine levels which are low in DM and prevent undue sympathetic tone in the central nervous system, thus suppresses of hepatic glucose synthesis. As a consequence there is reduction in post meal plasma glucose[61.]

BROMOCRIPTINE QR –MECHANISM OF ACTION.



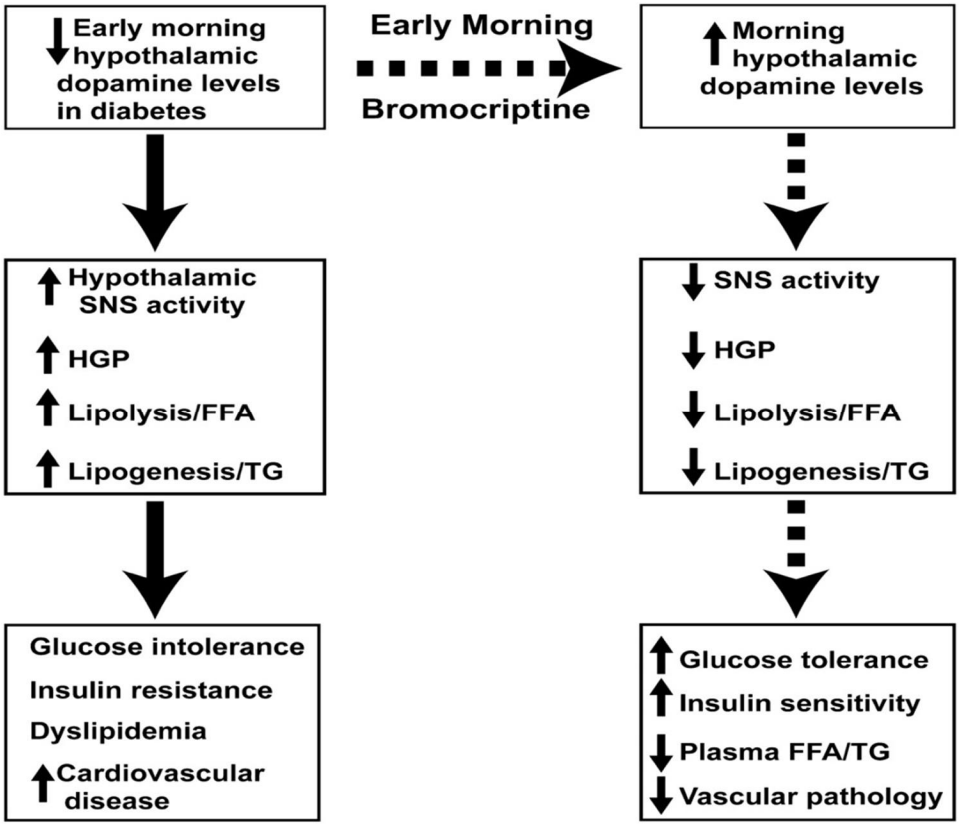
Bromocriptine Improves dopamine, which has a role in controlling metabolic effects. Drugs with antidopemenirgic effects like antipsychotic drugs show negative effects like increased insulin resistance, dyslipidemia and weight gain.

CENTRAL MECHANISM OF ACTION OF BROMOCRIPTINE.



Bromocriptine with dopaminergic effects show good metabolic profile, by decreasing blood glucose, dyslipidemia, and causing weight loss.

GLUCOSE HOMEOSTASIS AND INSULIN SENSITIVITY.



MIGRATING BIRDS & THRIFTY GENE HYPOTHESIS

The hypothesis behind obesity and insulin resistance is the thrifty gene hypothesis that is insulin resistance is an adaptive state of many vertebrate species in preparation for periods of hibernation, winter and famine.[63] During Evolution in animals, an increased body weight and insulin resistance was needed as protective during winter months or times of famine. The insulin resistant state ensures glucose supply to the central nervous system by increasing hepatic glucose output and by decreasing peripheral glucose utilization .it also raises lipolytic action for peripheral use.

Animals then revert back to an insulin sensitive condition when there is abundance of food. These changes in body weight and insulin resistance depending on season are due to changes in hypothalamic neuroendocrine rhythms [64].The serotonin and noradrenalin levels in the ventromedial hypothalamus are increased when there is the insulin resistant state. Bromocriptine reduces noradrenergic as well as serotonergic activity on ventromedial hypothalamus and reverses the insulin resistant state when given systemic or intracerebroventricular route in animals.

In humans, similar change in these neuroendocrine rhythms results in the non-seasonal development of obesity. The metabolic modifications such as insulin resistance, increased hepatic glucose output and increased lipolysis) which are needed in times of fasting or famine occurs in other period also .As a consequence there is an increased blood sugar and dyslipidemia in type 2 diabetic patients.

Reason for giving Bromocriptine in the morning:

In Type 2 diabetes mellitus patients the dopamine levels are lower in the morning when matched to nondiabetic population, leading to augmented sympathetic activity. The Bromocriptine quick release variant is usually given in the morning to reimburse for morning dip of dopamine. This Bromocriptine given in the morning augments this low hypothalamic dopamine levels and thereby inhibits the excessive sympathetic activity within the central nervous system.

Studies also shows Bromocriptine causes decrease in BP and decrease in adverse cardiovascular events. In some studies the results show insignificant effect of Bromocriptine on weight, however in all studies Bromocriptine does not cause weight gain[64]. Bromocriptine (Ergo set) reduces body weight. By the chronological interaction with circadian oscillations of neuroendocrine system, Bromocriptine modifies neurotransmitter action in the brain and improves glycemic control and insulin resistance in animal models of obesity and diabetes.[65].

Hence by all these mechanisms Bromocriptine reduces blood sugar of studies support inhibitory effects of dopamine on insulin secretion [by Bromocriptine s agonist action on dopamine receptor.

BENEFITS OF BROMOCRIPTINE

Bromocriptine is a well-known drug for the treatment of Parkinson's disease, hyperprolactinemia or acromegaly. In 2009 Bromocriptine quick release variant was approved in the USA for the treatment of type 2 diabetes mellitus. Bromocriptine induces positive metabolic effects such as decreasing

blood glucose and serum lipid profile and positive effect on body weight, blood pressure and cardiovascular events. The benefits of Bromocriptine are of greater utility in obese type 2 DM. The peculiar advantage of Bromocriptine is that it does not causes hypoglycemia.

Being a dopamine receptor (D2) agonist, it can reduce sympathetic activity and circulating NE levels. Thus it helps in the management of high blood pressure and LVH in patients with CKD. some research studies establishes that the low dose Bromocriptine causes blood pressure control and reduces LV mass in both peritoneal dialysis and hemodialysis patients and thus shows cardio protective effects[66].

In addition, BEC also has metabolic effects, reducing insulin resistance and improving glycemic control in overweight and patients with T2DM. Quick-release BEC was approved by the US Foodland Drug Administration for the management of T2DM [67, 68, 69.] Several studies demonstrated the beneficial effects of Bromocriptine on psoriatic skin lesions, psoriatic arthritis, and autoimmune diseases such as systemic lupus erythematous, rheumatoid arthritis, Reiter's syndrome and uveitis.[70, 71, 72.]

Several randomized controlled trials (mostly combining Bromocriptine with other oral glucose lowering medication) show a significant reduction in several metabolic parameters such as a 0.4-0.7% reduction in HbA1c[73]

Bromocriptine apart from improving glycemic control it reduced body fat stores, thus diminishing the need for oral hypoglycemic agents in obese type 2 diabetic patients. [74.]

AIMS AND OBJECTIVES

Aim

To evaluate the efficacy and safety of Bromocriptine in Type 2 Diabetes Mellitus.

Objectives

Primary objective:

To assess the efficacy of Bromocriptine as an add on therapy in lowering the Blood sugar level in known Type 2DM patients taking metformin and glipizide with poor glycemic control.

Secondary objective

To evaluate the safety of Bromocriptine as add on therapy with metformin & glipizide in T2DM patients with poor glycemic control.

MATERIALS AND METHODS

STUDY DESIGN:

A prospective, open labeled, comparative, randomized controlled study.

STUDY CENTER:

Department of General medicine – Diabetic OPD .Government Chengalpattu medical college and Hospital, **Chengalpattu.**

DURATION OF THE STUDY: **one year**

2014-2015.

PERIOD OF STUDY

3 months per patient.

STUDY POPULATION

Patients with Type 2DM attending diabetic OPD.

SAMPLE SIZE

60 patients in each group.

SELECTION CRITERIA

Inclusion criteria

- Known T2DM for more than 5 years *patients* with Fasting blood sugar more than 126mg% and post prandial blood sugar more than 200mg%

- Known T2DM for more than 5 years taking metformin 500mg bd and glipizide 5mg bd
- Sex: both male and female patients.
- Age 30-60 years
- Patients who are willing to give informed consent.

Exclusion criteria

- All cases of Type 1DM
- Pregnant & lactating women
- Age < 30 years and >60 years of old.
- patients with FBS>300mg/dl AND PPBS> 400 mg/dl and HbA1C >10%
- Patients in whom insulin is indicated for treatment
- Patients associated with renal & liver disease
- Patients with coronary arterial disease, CCF, migraine, PVD
- Patients with known hypertension > 140/90mmhg
- Any concurrent intake of sympathomimetic drugs
- Any other serious medical or surgical illness.

STUDY PROCEDURE:

Ethical consideration:

- This study was conducted after getting approval of institutional ethical

committee. The study was conducted as per GCP guidelines.

- 200 Adult Type 2 DM patients fulfilling the inclusion criteria were included in the study. Patients attending the OPD of diabetology department, Chengalpattu medical college hospital were explained in detail about the study procedure, purpose, benefit & possible risks in regional language.

- Written informed consent got from the patients who were willing to participate in the study. Patient information sheet and consent form were in regional language {Tamil} and also in English for people who know only English. Patients who were illiterate were explained about the study and left thumb impression obtained from them in the presence of impartial witness.

SCREENING

After getting informed consent, 200 patients with type 2DM, FBS[>126mg% and PPBS> 200 mg%] and already on metformin 500mg bd & Glipizide 5mg bd were screened as follows. Detailed clinical history and demographic particulars were collected from all patients.

- Age, Gender, Bodymassindex, clinical examination details were recorded for each patient.

- Baseline investigations, Hemoglobin, total count, differential count, Erythrocyte Sedimentation Rate (ESR), LFT, Blood urea, serum

creatinine, blood lipid profile, urine routine were done and recorded for each patient. Chest XRAY, ECG was taken for each patient.

Recruitment & Randomization

After screening 200 patients, 130 who fulfilled the selection criteria were recruited for the study.

All the odd number patients were allocated into control group and all the even number of patients were allocated into study Group.

All the patients were advised to follow the diet chart and 30-45 minutes of moderate aerobic activities 3-5 days per week.

Study Group

Patients already on metformin 500mg bd & Glipizide 5mg bd were added Bromocriptine 1.6mg od for a period of 12 weeks.

Bromocriptine Priscription[75]

Daily morning Bromocriptine 0.8 mg OD within 2 hrs of waking ,for initial 1 week, followed by single morning dose of 1.6 mg/day within 2hrs of awaking for next 11 weeks was prescribed.

Control Group

Patients already on metformin 500mg bd & Glipizide 5mg bd are continued with the same for next 3 months.

TREATMENT SCHEDULE:

Control Group A

METFORMIN 500mg BD +GLIPIZIDE 5 mg BD + BROMOCRIPTINE 1.6 mg OD for a period of 12weeks.

Study Group B:

METFORMIN 500mg BD +GLIPIZIDE 5 mg BD for a period of 12weeks.

FOLLOW UP VISITS:

After baseline investigations and clinical examination the patients in each group. Group A [control group] and group B [study group] were given medications for 2 weeks. At the end of every 2 weeks patients were advised to return back the empty packs of medicines to assure compliance. After getting clinical history and clinical examination patients were given medicines for next 2weeks.At the end of each month Fasting Blood sugar and postprandial blood sugar were collected for each patient. This was done repeatedly for 3 months. Adverse effects were noted during every visit and if any serious adverse affects patients were asked to report immediately to hospital and investigator.

At the end of 3rd month FBS, PPBS and Hba1c were done. Also baseline blood investigations done at the end of 3 months. After this Patients were advised to follow their regular drugs after the study and dosage adjusted according to their blood glucose level. Patients were monitored for any adverse effects for 2 weeks after withdrawal of Bromocriptine.

ASSESMENT OF EFFICACY OF BROMOCRIPTINE:

1. Was done by measuring for each patient in the both study group and control group at baseline, 1st month, 2nd month and at 3rd month.

2. Hba1c was done at baseline [at the start of the study] and at the end of the study for each patient in both study and control group. By comparing the results of each group the efficacy of Bromocriptine in decreasing HbA1C was evaluated.

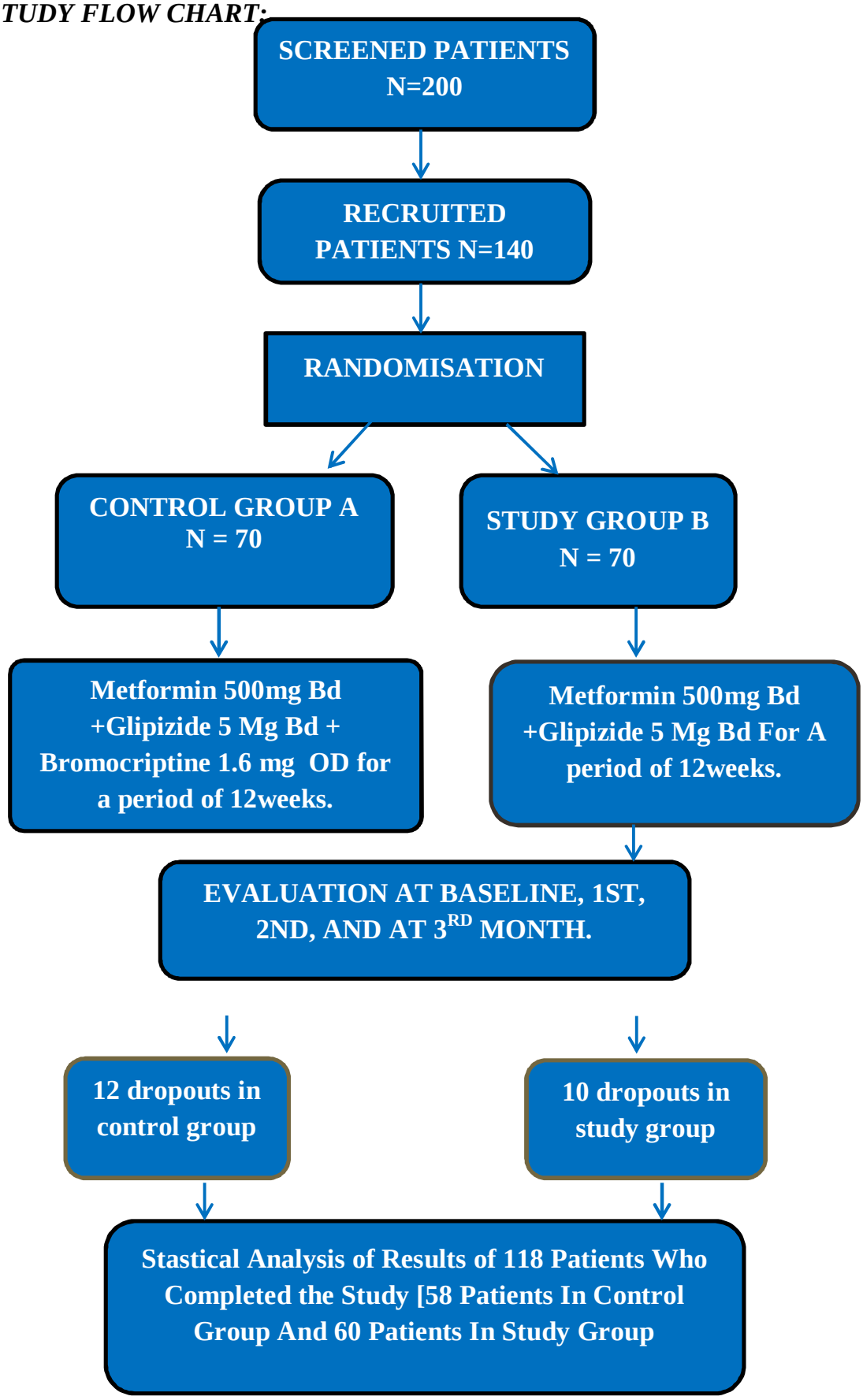
ASSESESMENT OF SAFETY OF BROMOCRIPTINE:

1. Patients were advised to report any adverse effects immediately and at each visit to the investigator.

2. Blood pressure monitoring, baseline laboratory investigations, Hemoglobin, total count, differential count, Erythrocyte Sedimentation Rate(ESR) ,LFT, Blood urea, serum creatinine, blood lipid profile, urine routine ,Chest XRAY, ECG were done and recorded for each patient at the start of the study and compared to the same tests done at the end of the study.so that the cardiac, renal ,pulmonary and hepatic adverse effects and effect on lipid profile was evaluated before and after the study period.

3. The data from investigations were collected, tabulated and analyzed stastically.

STUDY FLOW CHART:



RESULTS

Totally 200 patients with T2DM was screened for this study. Out of 200, 38 patients had hypertension 12 had Dyslipidemia 10 patients had elevated serum creatinine levels. These 60 patients were excluded from the study. 140 patients who satisfy the inclusion criteria were recruited for this study.

Out of 140 patients, only 118 patients completed the study. 14 patients were lost to follow up. 8 patients were withdrawn from the study due to side effects. Of the 8 patients,4 developed hypoglycemia frequently (2 in group A , 2 in group B) and 4 patients had , nausea and vomiting . (1 in group a, 3 in group B). Only 118 patients completed the study, results of those 118 patients were analyzed stastically. Statistical analysis was done with paired and unpaired t test. Age distribution and sex distribution were analyzed using: PEARSON CHISQUARE TEST. Stastical package for social sciences -SPSS 16 was used for stastical analysis of results.

Table 1a: Number of Patients Completed And Number Of Dropouts

Groups	Total no of patients	No. of patients completed the study	No of dropouts [22]	
			Lost	Side effects
Group A [control group].	70	58	9	3
Group B study group	70	60	5	5
Total	140	118	14	8

Table 1A shows total number of patients who completed the study and total number of drop outs from the study in both control group and study group.

Table 1b: Age Distribution

Age in years	Control		Study		Pearson Chi Square Test
	N	%	N	%	
30-40	4	6.7O	6	10	X^2 =1.06 P=0.78
41-50	14	23.30	15	25	
51-60	34	58.30	30	50	
>61	6	11.70	9	15	
TOTAL	58	100	60	100	

p≤ 0.05 is significant; p≤0.01 is highly significant; p≤ 0.001 very highly significant.

Table 2 displays no stastically significant difference both control and study groups regarding distribution of age

Figure 1: Age Distribution of Control And Study Groups

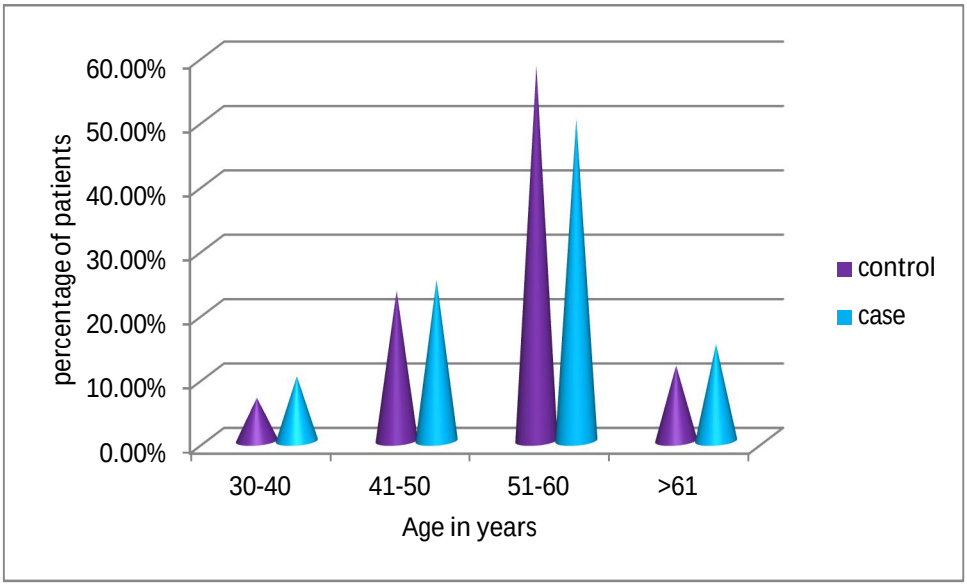


Figure 1shows age distribution among control and study groups

Table 2: Sex Distribution

Gender	Control		Study		Pearson Chi Square Test
	N	%	N	%	X^2= 0.134 P=0.7
F	32	55%	31	51.7%	
M	26	45%	29	48.3%	
Total	58	100%	60	100%	

p≤ 0.05 is significant; p≤0.01 is highly significant; p≤ 0.001 very highly significant.

Table 2 shows no stastically significant difference both control and study groups regarding distribution of gender.

Figure 2: Sex distribution of control and study groups.

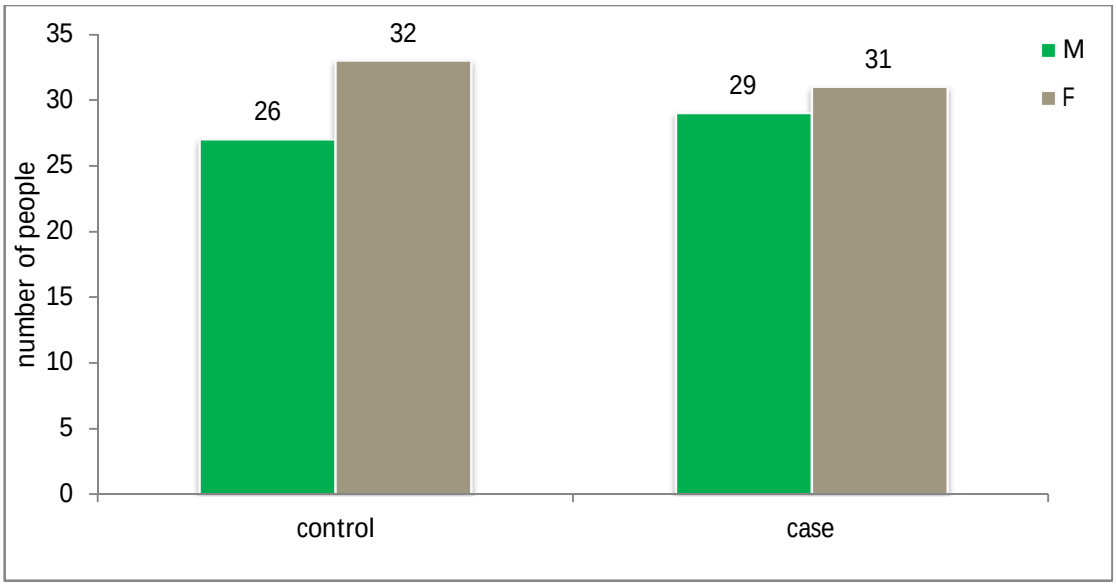


Figure 2 shows sex distribution among control and study groups.

Table 3: Body Mass Index Distribution

Body mass Index	Control		Study		Students independent t test
	Mean ±	SD	Mean±	SD	
Baseline	26.36 ±	2.389	26.03±	2.02	P=0.42
After 3months	26.1±	2.456	26.01±	2.045	P=0.825
Paired T test	P=0.06		P=0.19		

p≤ 0.05 is significant; p≤0.01 is highly significant; p≤ 0.001 very highly significant

Figure 3: Body mass index distribution of control and study groups.

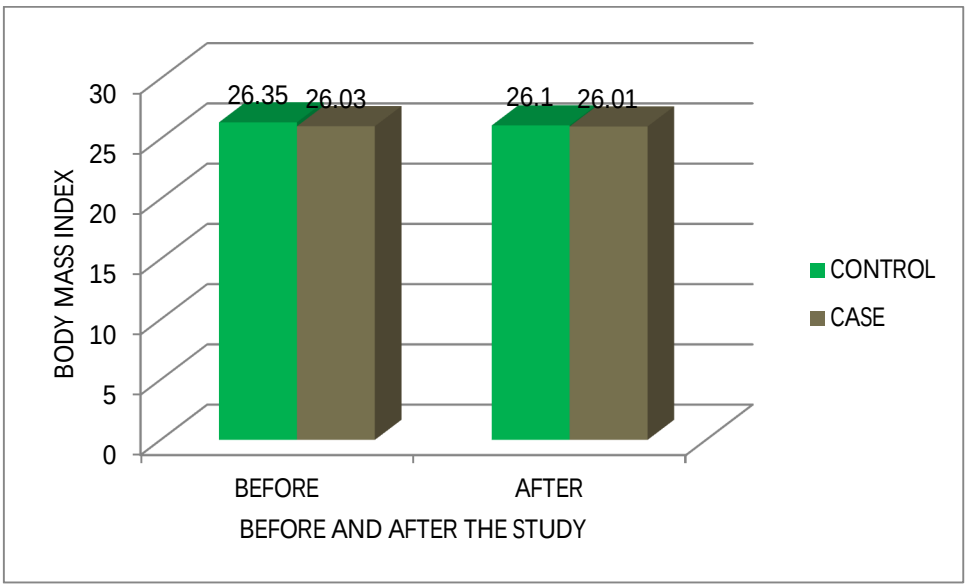


Figure 3 shows BMI distribution before and after the study.

Table 3 and figure 3 shows BMI Distribution at the start of the study and after 3 months. No statistically significant difference between study & control groups in mean BMI before drug administration at the start of the study.

At the end of the study there is a mild decrease in mean BMI in both control and study groups. The decrease in BMI in the study group and control group is not stastically significant.

EVALUATION OF EFFICACY OF BROMOCRIPTINE IN DECREASING BLOOD SUGAR:

Table 4: Fasting blood sugar of control and study groups.

Month	Fasting Blood Sugar	Control	Study	Student Independent "t test"
		Mean ±sd	Mean±sd	
0 month	Baseline	188.17±47.461	179.8±34.018	P=0.27
I month	Visit 1	179.1±47.322	161.67±43.422	**P=0.038***
II month	Visit 2	180.2±52.371	151.558±38.729	**P=0.001****
III month	Visit 3	164.6±46.466	131.65±27.042	**P=0.0001*****

Table 4a: Fasting Blood Sugar [Before and After Study]

Fasting Blood Sugar	Control	Study
	Mean ± SD	Mean ± SD
At baseline	188.17±47.461	179.8±34.018
After 3 months	164.6±46.466	131.65±27.042
Paired t test	T=6.79**, p = 0.0001**	T=15.3,**p=0.0001**

*P ≤ 0.05 Significant; ** P≤0.01 highly significant ***P≤0.001 very highly significant

Table 4 shows mean FBS of control and study groups at baseline and at every visit.

Table 4A displays the comparison of mean FBS before and after 3 months in both control and study groups.

Figure 4: Fasting Blood Sugar of Control And Study.

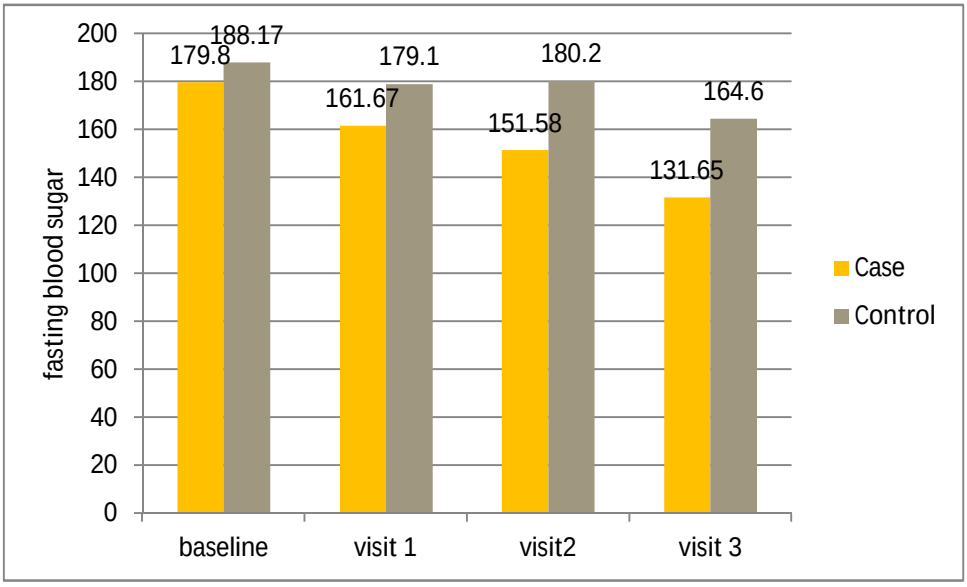


Table 4,4a And Figure 4 demonstrate there is no statistical difference between mean FBS at baseline in control and study groups. But there is stastically significant difference in mean FBS between control and study groups at subsequent visits. [Students independent t test was used].

At the end of the study there is decrease in mean FBS in both study and control groups.

Controlgroup: Decrease of mean FBS seen from baseline 188.17 to 164.6[23.57] after 3 months

Study Group: Decrease of mean FBS seen from baseline 179.8 to 131.65[48.15] after 3 months

When paired t test was used to compare mean FBS before and after drug administration statistically significant reduction is seen in study group **(P=0.0001)** and also in control group **(P=0.0001**) at the end of the study.

Table 5- Postprandial Blood sugar of Control And Study Groups

Month	Postprandial Blood Sugar	Control	Study	Student Independent "t test"
		Mean ± sd	Mean ± sd	
0 month	BASELINE	281.55±55.984	297.82±58.447	P=0.122
I month	Visit 1	227.72±60.964	269.4±57.035	**P=0.00001*** **
II month	Visit 2	223.95±59.741	261.70±64.498	**P=0.001** **
III month	Visit 3	252.37±63.43	221.38±59.65	**P=0.007** **

Table 5a- Postprandial Blood sugar [Before And After Study]

Postprandial blood sugar	Control	Study
	Mean ± sd	Mean ± sd
At baseline	281.55±55.984	297.82±58.447
After 3 months	252.37±63.43	221.33±59.65
Paired t test	T=6.09**,p=0.0001**	T=16.63,p**=0.0001**

P ≤ 0.05 Significant; ** P≤0.01 highly significant ***P≤0.001 very highly significant

Table 5 shows mean PPBS of control and study groups at baseline and at every visit. Table 5A displays the comparison of mean PPBS before and after the study in both groups. [Control and study group]

figure 5: Postprandial blood sugar of control and study groups.

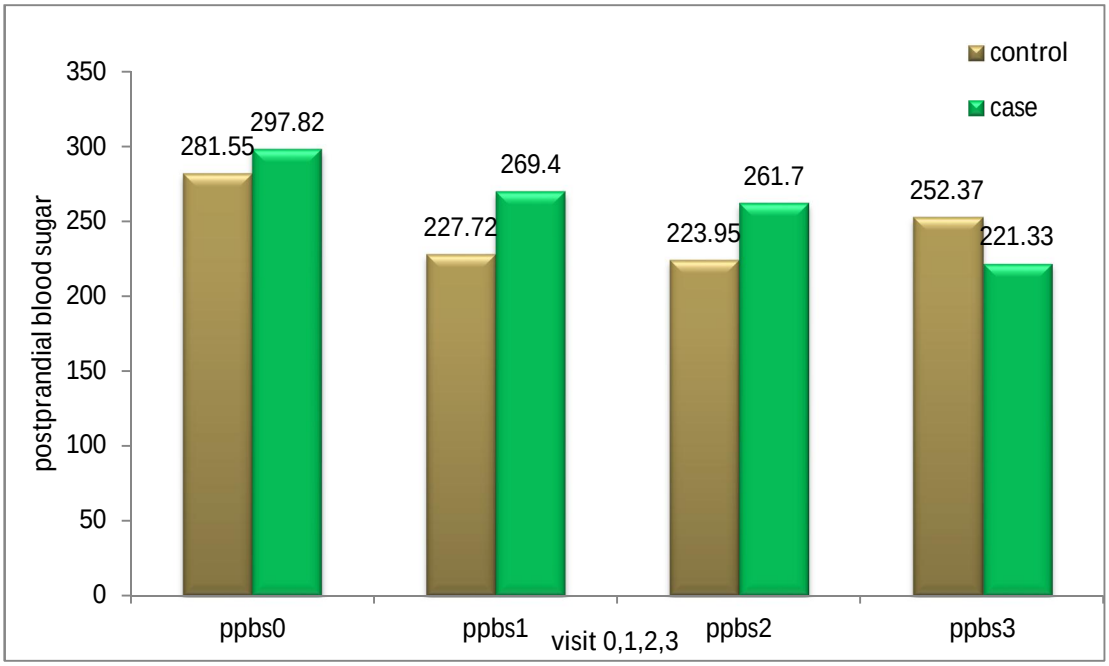


Table 5,5a and Figure 5 demonstrate there is no statistical difference between mean PPBS at baseline in control and study groups. But there is stastically significant difference in mean PPBS between control and study groups at subsequent visits.

At the end of the study there is decrease in mean PPBS in both study and control groups.

Controlgroup: Decrease of mean PPBS seen from baseline 281.55 to 252.37[29.18] after 3 months.

Study Group: Decrease of mean PPBS seen from baseline 297.82 to 221.33[76.49] after 3 months.

When paired t test was used to compare mean PPBS before and after drug administration statistically significant reduction is seen in study group at the end of the study **[P = 0.0001**]and also in the control group.[**p=0.0001].**

Table 6 : HbA1c [Before and After Study]

HbA1c	Control	Study	Student independent t test
	Mean ± SD	Mean ± SD	
Baseline	7.632±0.688	7.54±0.618	P=0.445
After 3 months	7.325±0.667	7.015±0.542	**P=0.006**
Paired t test	**P=0.001**	**P=0.0001**	

*P ≤ 0.05 Significant; ** P≤0.01 highly significant ***P≤0.001 very highly significant.

Figure 6: HbA1c Before And After Study in Both Groups

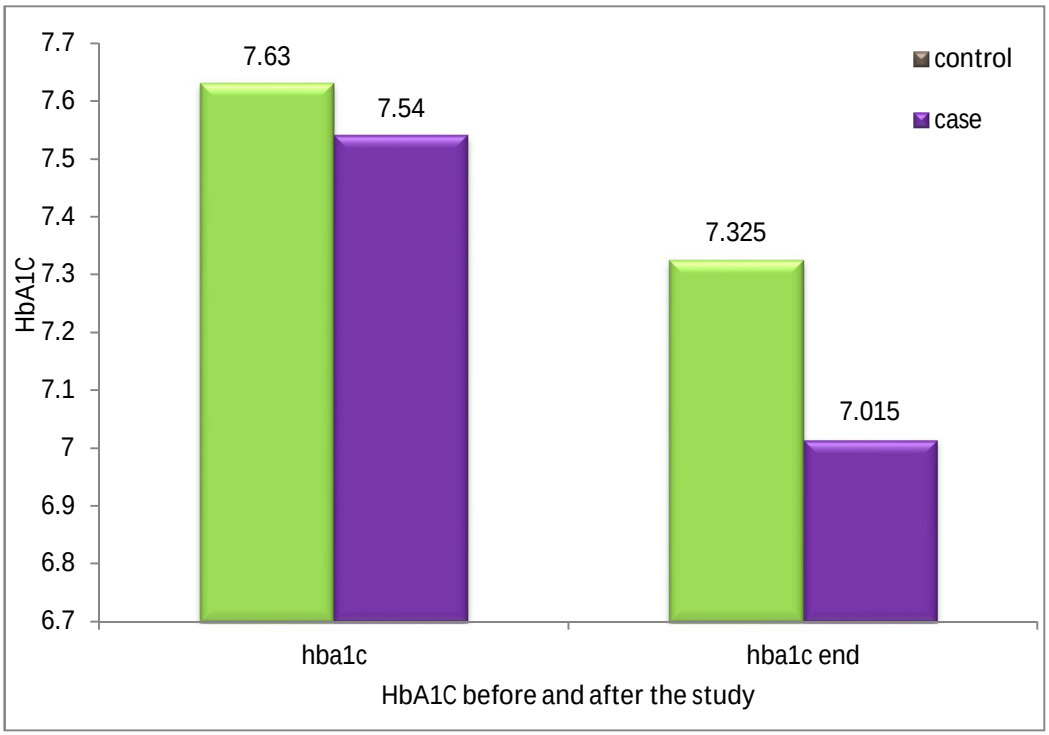


Table 6 and Figure 6 displays the comparison of mean HbA1C before and after the study in both groups. . [Control and study group].

Table 6 & Figure 6 demonstrate that there is no statistical difference between mean HbA1C at baseline in control and study groups. But there is stastically significant difference in mean HbA1C between control and study groups at the end of 3 months. [P=0.006][Student independent t test is used]

At the end of the study there is a decrease in mean HbA1C in both study and control groups.

Control group: Decrease of mean HbA1C seen from baseline- 7.63 to 7.32 [0.3] after 3 months.

Study Group: Decrease of mean HbA1C seen from baseline - 7.54 to 7.01 [0.5] after 3 months.

When paired t test was used to compare mean HbA1C before and after drug administration statistically significant reduction is seen in the study group and in the control group at the end of the study. The reduction in the study group is higher [**p=0.0001**] than the control group [**p=0.001]** at the end of the study.

Table 7: total cholesterol before and after the study.

Total Cholesterol	Control	Study	Student Independent "t test"
	Mean ± SD	Mean ± SD	
Baseline	243.22±44.394	254.85± 27.296	P=0.085
After3 months	241.72±43.985	247.22.± 25.634	P=0.402
Paired t test	**P=0.003**	**P=0.0001**	

*P ≤ 0.05 Significant; ** P≤0.01 highly significant ***P≤0.001 very highly significant.

Figure 7: Total cholesterol before and after the study in both groups

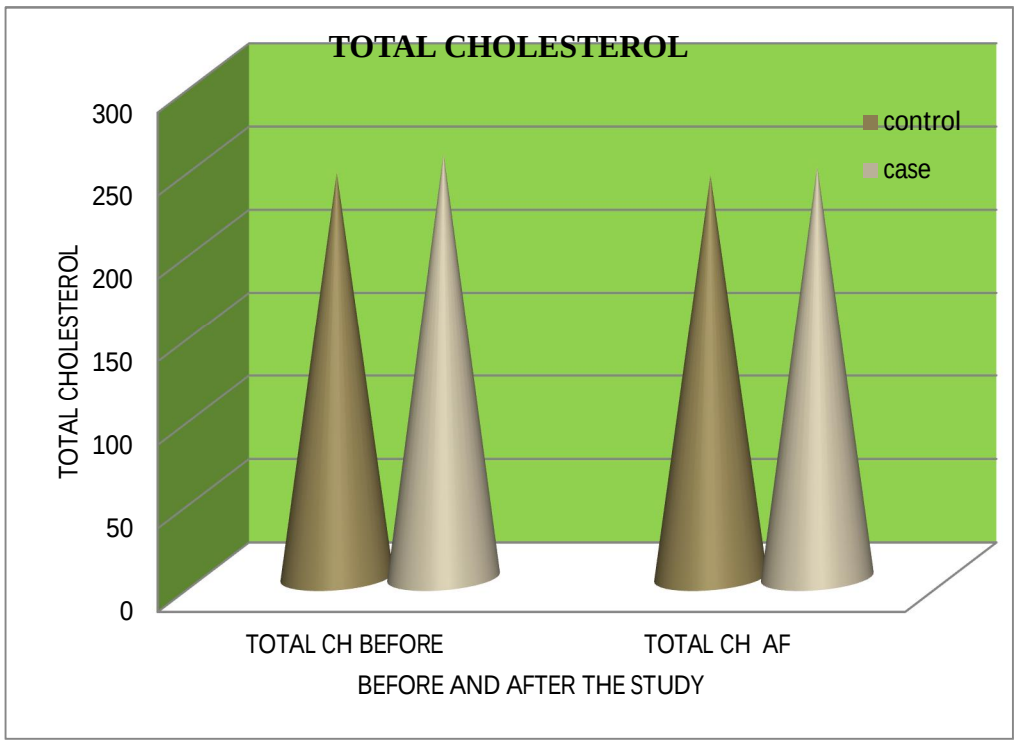


Table 7 and Figure 7 displays the comparison of mean Total cholesterol before and after 3months between control and study group.

Table 7 and Figure 7 demonstrates there is no statistical difference between mean Total cholesterol at baseline in control and study groups.

At the end of the study there is decrease in means total cholesterol in both study and control groups.

Control group: Decrease of mean total cholesterol seen from baseline 243.22 to 241.72 [1.5] after 3 months.

Study Group: Decrease seen of mean total cholesterol from baseline 254.85 to 247.22[7.6] after 3 months.

When paired t test was used to compare mean total cholesterol before and after drug administration statistically significant reduction is seen in study group [p=0.0001] and the control group [p=0.003] at the end of the study. But the reduction is more in the study group than the control group.

Table 8- LDL before and after the study

LDL	Control	Study	Student Independent "t test"
	Mean ± SD	Mean ± SD	
Baseline	160.1±35.384	173.67±26.648	P=0.019
After 3 months	160.03±34.329	166.3±26.626	P=0.266
Paired t test	P=0.7	**P=0.001**	

*P ≤ 0.05 Significant; ** P≤0.01 highly significant ***P≤0.001 very highly significant.

Figure 8: LDL before and after the study in both groups

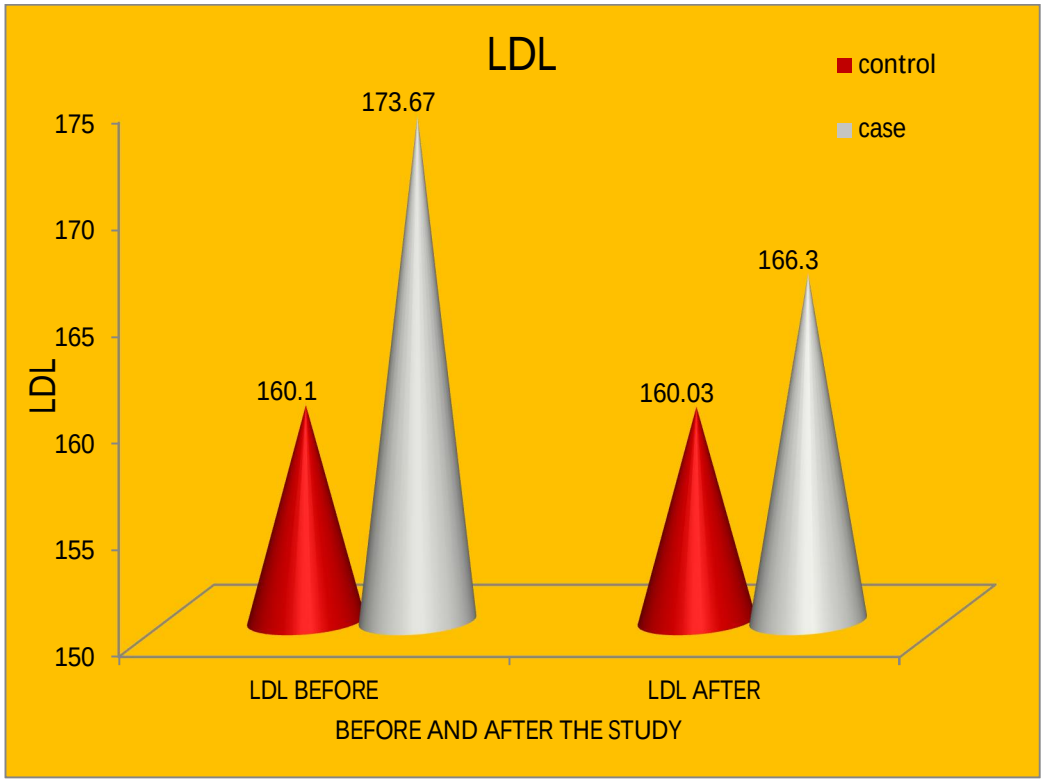


Table 8 and Figure 8 displays the comparison of mean LDL between the Control and study groups before and after the study.

Table 8 and Figure 8 demonstrates there is no statistical difference in mean LDL at baseline between control and study groups...

At the end of the study there is decrease in mean LDL in both study and control groups.

Control group: Decrease of mean LDL from baseline- 160.1 to 160.3 [0.2] after 3 months.

Study Group: Decrease of mean LDL from baseline -173.6 to 166.3 [7.37] after 3 months.

When paired t test was used to compare mean LDL before and after drug administration, statistically significant reduction is seen in study group at the end of the study [**P = 0.001]**. The reduction in control group is not statistically significant [P=0.7].

Table 9: VLDL before and after the study

VLDL	Control	Study	Student Independent "t test"
	Mean ± SD	Mean ± SD	
Baseline	44.68±23.898	35.2±9.892	P=0.006
After3 months	43.8±21.812	34.73±8.986	**P=0.004**
Paired t test	P=0.3	P=0.2	

*P ≤ 0.05 Significant; ** P≤0.01 highly significant ***P≤0.001 very highly significant.

Figure 9: VLDL before and after the study in both groups.

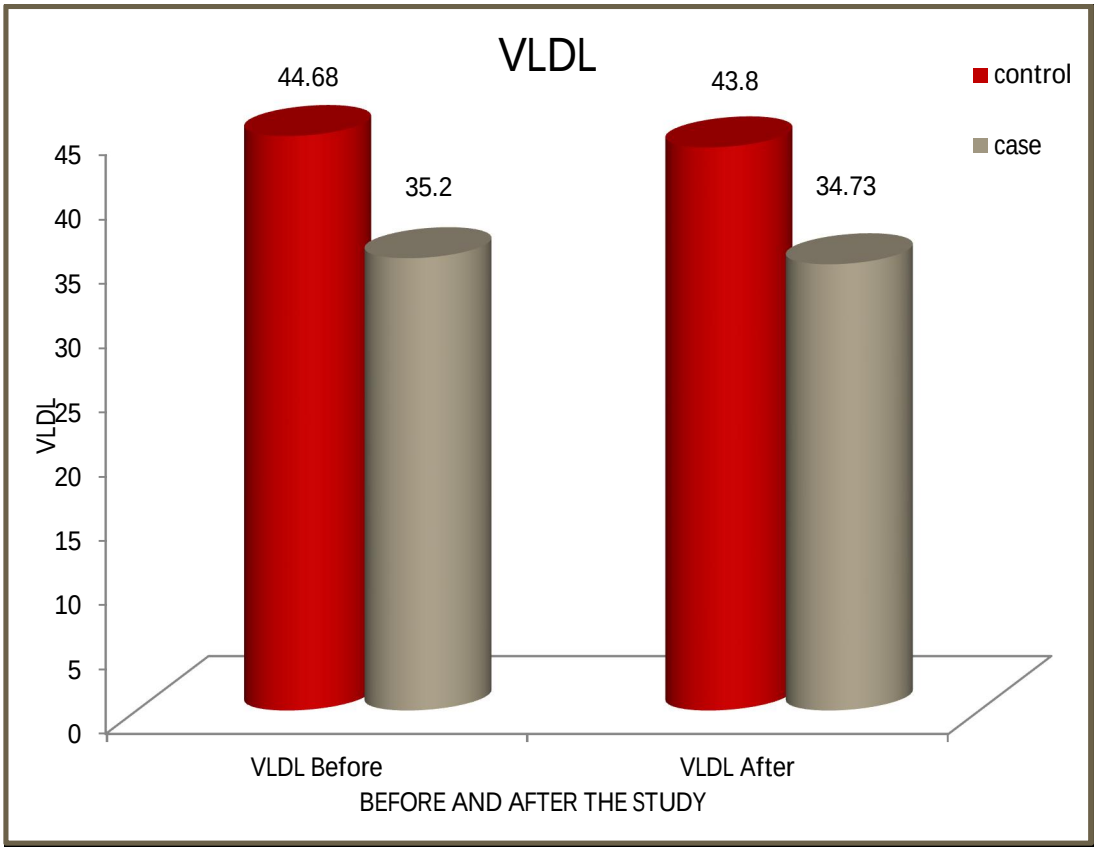


Table 9 and Figure 9displays the comparison of mean VLDL before and after he study in both groups. [Control and study group]

Table 9 And Figure 9 demonstrates there is no statistical difference between Mean VLDL at baseline in control and study groups. But there is stastically significant difference in mean VLDL score between control and study groups **[P=0.004]** at the end of 3 months. [STUDENTINDEPENDENT "t test"].

Control group: Decrease seen from baseline 44.68-43.8 [0.88] after 3 months.

Study Group: Decrease seen from baseline 35.2-34.73[0.47] after 3 months.

At the end of the study there is the mild decrease in mean VLDL in both study and control groups. When paired t test was used to compare mean VLDL before and after drug administration the decrease in mean VLDL is not stastically significant in both groups.

Table 10 - TGL Before and After ahe Study

TGL	Control	Study	Student Independent "t test"
	Mean ± SD	Mean ± SD	
Baseline	178.9±26.476	176.15±34.584	P=0.674
After3 months	177.44±27.023	166.2±35.773	P=0.064
Paired t test	P=0.06	**P=0.001**	

*P ≤ 0.05 Significant; ** P≤0.01 highly significant ***P≤0.001 very highly significant.

Figure 10: TGL before and after the study in both groups.

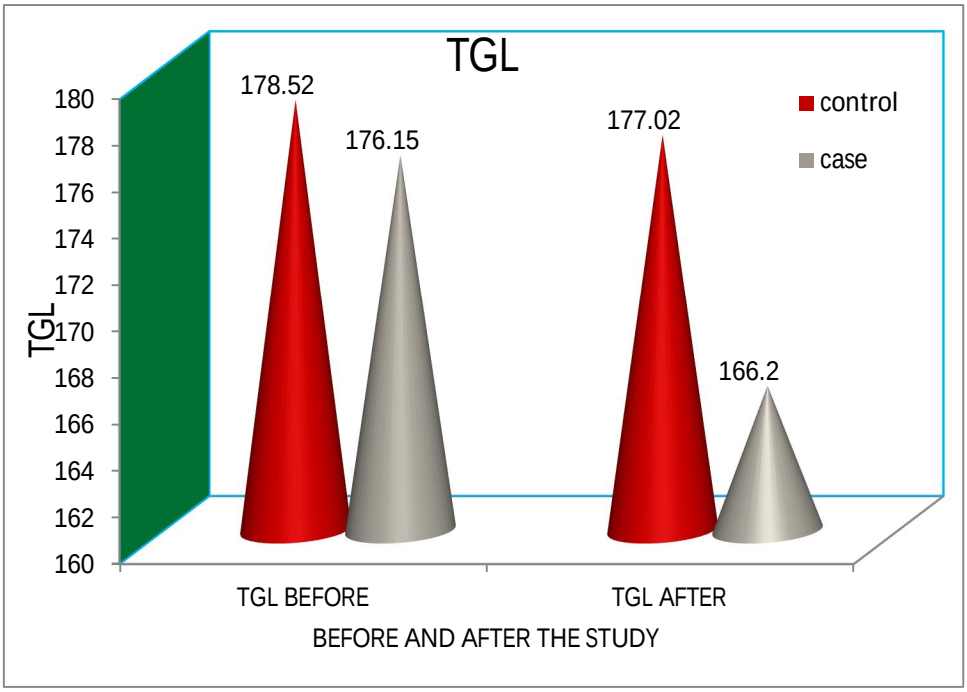


Table 10 and Figure 10 displays the comparison of mean TGL before and after 3 months between Control and study group.

Table 10 and Figure 10 demonstrates there is no statistical difference between mean TGL at baseline in control and study groups. Also there is no stastically significant difference in mean TGL scores between control and study groups. [Student Independent “t test”] at the end of the study.

At the end of the study there is the decrease in mean TGL in both study and control groups.

Control group: Decrease seen from baseline 178.9-177.44 [1.46] after 3 months.

Study Group: Decrease seen from baseline 176.15 to 166.2 [9.95] after 3 months.

When paired t test was used to compare mean TGL before and after drug administration. In the study group the decrease in mean TGL is higher and statistically significant [**P = 0.001].**The decrease in mean TGL is not stastically significant in the control group. [P=0.06]

Table 11 -HDL before and after the study.

HDL	Control	Study	Student Independent "t test"
	Mean ± SD	Mean ± SD	
Baseline	39.85±9.426	38.65±8.81	P=0.502
After3 months	39.63±9.579	38.6±8.681	P=0.576
Paired t test	P=0.6	P=0.8	

*P ≤ 0.05 Significant; ** P≤0.01 highly significant ***P≤0.001 very highly significant.

figure 11: HDL before and after the study in both groups.

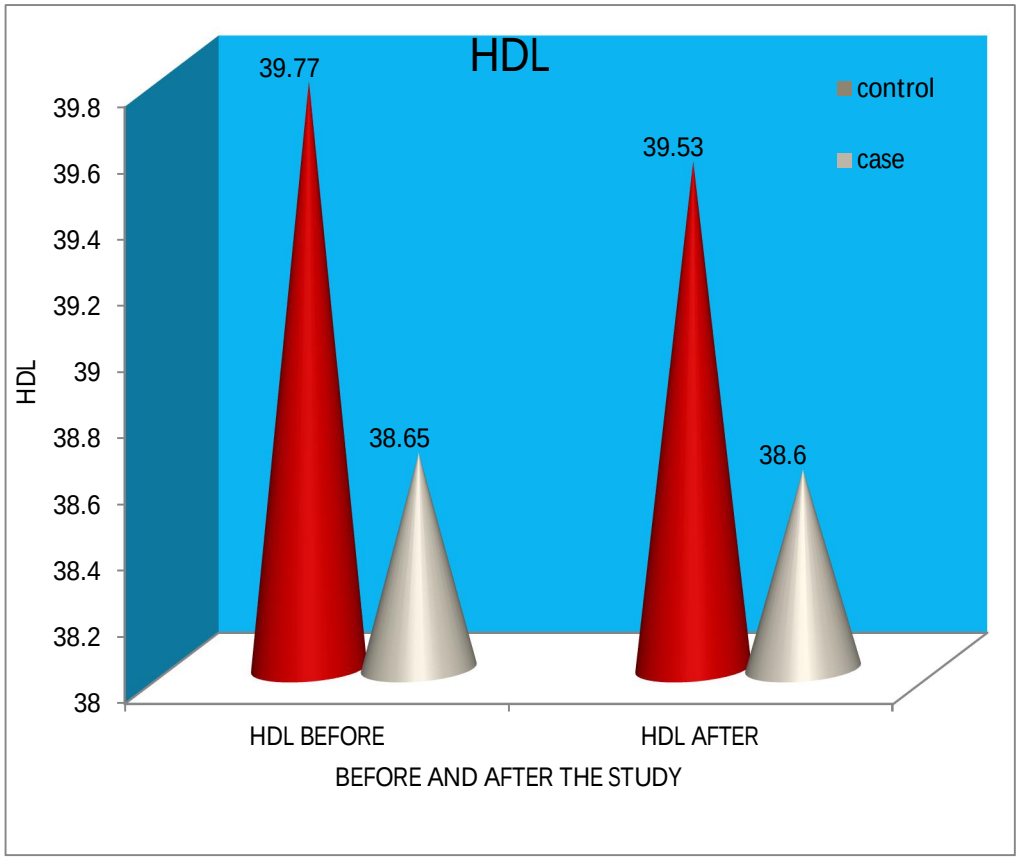


Table 11 and Figure 11 displays the comparison of mean HDL before and after the study in both groups

Table 11 and Figure 11 demonstrates there is no statistical difference between mean HDL at baseline in control and study groups. Also there is no stastically significant difference in mean HDL between control and study groups at end of 3 months.

When paired t test was used to compare mean HDL before and after drug administration NO statistically significant change is seen in study group as well as the control group.

Table 12- Systolic BP before and after the study.

Mean SBP	Control	Study	Student Independent "t test"
	Mean ± SD	Mean ± SD	
Baseline	128.68±12.598	124.37±10.83	P=0.065
After3 months	124.98±9.887	122.5±9.13	P=0.201
paired t test	**P=0.001**	**P=0.001**	

*P ≤ 0.05 Significant; ** P≤0.01 highly significant ***P≤0.001 very highly significant.

Figure 12: Systolic BP Before and After the Study in Both Groups

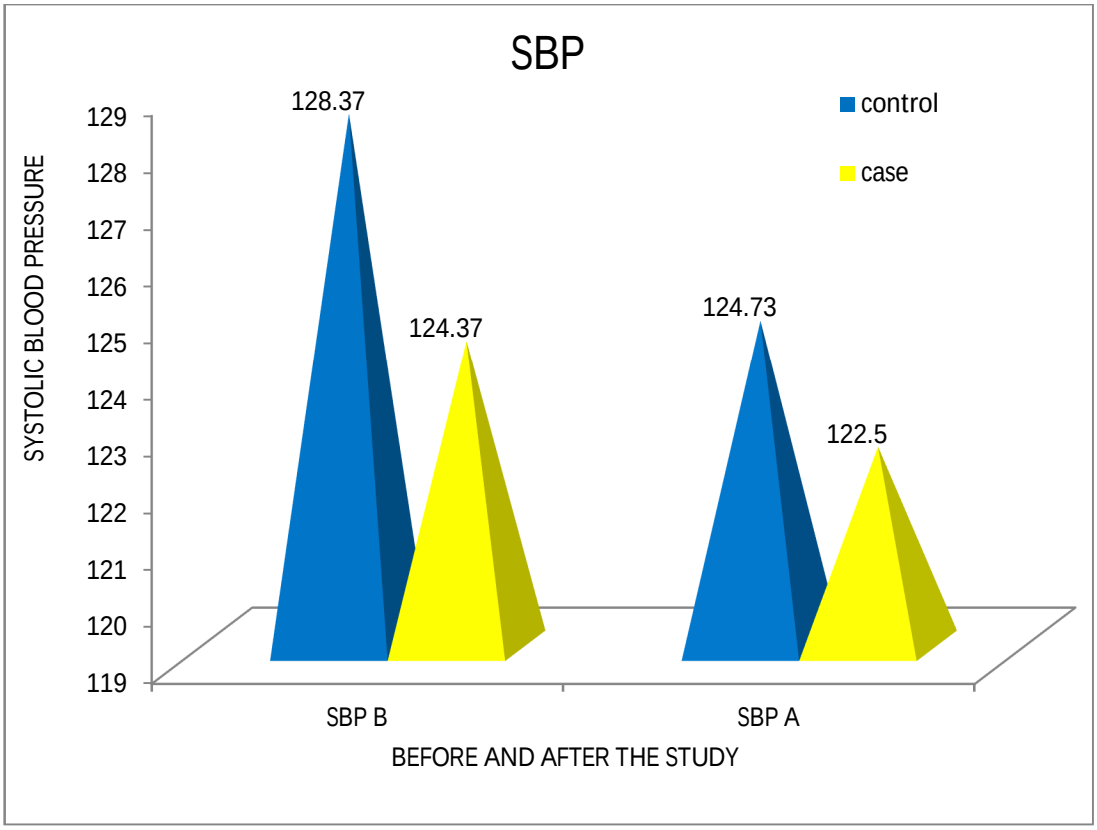


Table 12 and Figure 12 displays the comparison of mean SBP before and after 3 MONTHS between study and control groups.

Table 12 and figure 12 demonstrates there is no statistical difference between mean SBP at baseline in control and study groups. Also there is no stastically significant difference in mean SBP between control and study groups at the end of 3 months. [Student Independent "T Test"].

At the end of the study there is the decrease in mean SBP in both study and control groups.

Control group: Decrease seen from baseline 128.68-124.98[3.64] after 3 months.

Study Group: Decrease seen from baseline 124.37-122.5[1.87] after 3 months.

When paired t test was used to compare mean SBP before and after drug administration the decrease in mean SBP is [**P =0.001]** stastically significant in control group as well as study group. [P **=0.001]**

Table: 13 Diastolic BP before and after the study.

DBP	Control	Study	Student Independent "t test"
	Mean ± SD	Mean ± SD	
Baseline	83.05±8.59	79.97±7.987	P=0.062
After3 months	80.44±6.369	78.83±7.386	P=0.214
Paired t test	**P=0.002**	**P=0.0001**	

*P ≤ 0.05 Significant; ** P≤0.01 highly significant ***P≤0.001 very highly significant.

Figure 13: **Diastolic BP Before and After the Study in Both Groups**

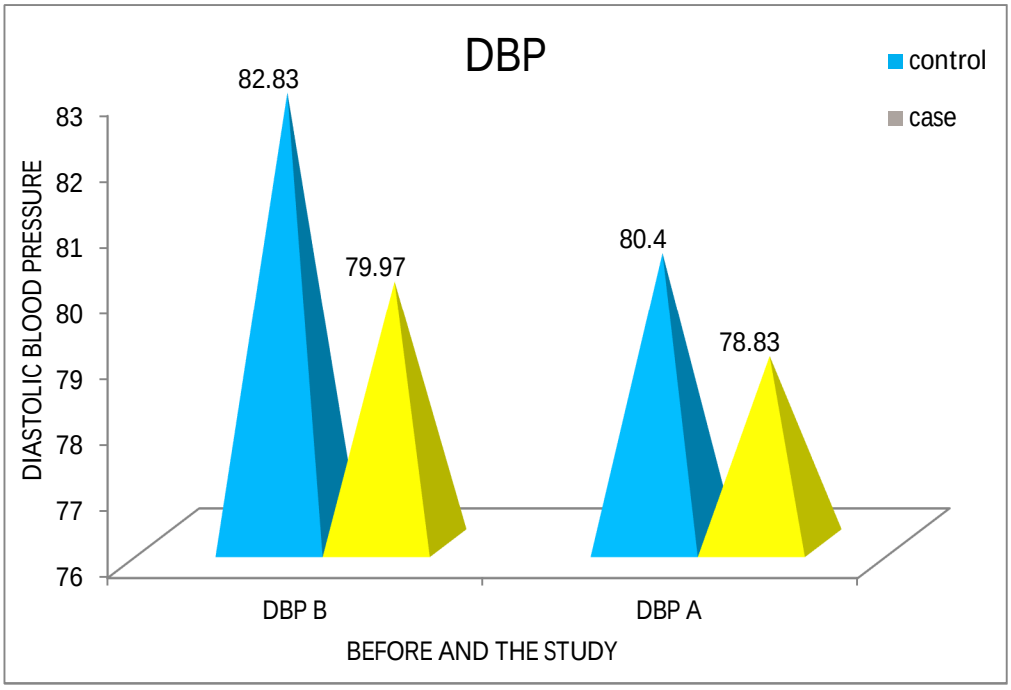


Table 13 and Figure 13 displays the comparison of mean DBP before and after the study in both groups.

Table 13 and Figure 13 demonstrates there is no statistical difference between mean SBP at baseline in control and study groups. Also there is no stastically significant difference in mean DBP between control and study groups at the end of 3 months. [Student Independent "T Test"].

At the end of the study there is decrease in mean DBP in both study and control groups

Control group: Decrease seen from baseline 82.83 to 80.4[2.43] after 3 months.

Study Group: Decrease seen from baseline 79.9 to 78.83 [1.14] after 3 months.

When paired t test was used to compare mean DBP before and after drug administration the decrease in mean DBP is [**P = 0.0001**] stastically significant in study group and also stastically significant in control group. [**p=0.002].**But the decrease in mean DBP is higher in study group than control group.

Table 14: Comparison of Reduction Between Control and Study Groups

Parameters	Reduction from baseline		student independent t' test
	Control	Study	
	Mean score at baseline minus mean score at the end	Mean score at baseline minus mean score at the end	
BMI	0.258	0.02	P=0.07
FBS	23.56	48.16	**P=0.0001**
PPBS	29.18	76.4	**P=0.0001**
HbA1C	0.30	0.52	**P=0.001**
Total Cholesterol	1.5	7.63	**P=0.0001**
TGL	1.5	9.95	**P=0.0001**
LDL	0.06	7.36	**P=0.0001**
VLDL	0.88	0.46	P=0.647
HDL	0.25	0.05	P=0.712
SBP	3.63	1.86	P=0.143
DBP	2.43	1.13	P=0.289

*P ≤ 0.05 Significant; ** P≤0.01 highly significant ***P≤0.001 very highly significant.

Table 14 Shows comparisons of reduction [from baseline to end of the 3 month] of parameters of control group with the reduction [from baseline to end of the 3 month] of parameters of study group.

The reduction of FBS, PPBS, HbA1C, total cholesterol, TGL and LDL in the study group is more than the reduction seen in the control group and it is statistically significant.

Table: 15 Comparisons of adverse events

Group	Adverse events		Total	Chi-square test
	Present	Absent		
Control	3	55	58	X^2=0.42 P =3.87
Study	5	55	60	

*P ≤ 0.05 Significant; ** P≤0.01 highly significant ***P≤0.001 very highly significant.

Table 15: shows the comparison of adverse events among groups and their stastical significance. 8 patients withdrawn from the study due to adverse effects. [3 in control group, 5 in study group]. Of the 8 patients,4 developed hypoglycemia frequently (2 in group A , 2 in group B) and 4 patients had , nausea and vomiting . (1 in group a, 3 in group B.

Table 16: **Side effects observed**

S .No	Side effects	Control group		Study group	
		N	%	N	%
1	Nausea, vomiting	1	1.7%	3	5%
2	Diarrhea	-	-	-	-
3	Giddiness	-	-	-	-
4	Headache	-	-	-	-
5	Hypoglycemia	2	3.4%	2	3.3%
6	Psychosis	-	-	-	-
7	Erythromelalgia	-	-	-	-
8	Orthostatic hypotension	-	-	-	-

Table 16 shows analysis of various adverse effects in control and study groups.

No stastically significant difference seen between the adverse effects of study and control groups.

BIOCHEMICAL EVALUATION OF SAFETY OF BROMOCRIPTINE.

Table 17: Shows the hematological and biochemical parameters of the control group and the study groups at the start and end of the study.

Parameter	Group	At the start	At the end	Student paired t- test
		Mean ± SD	Mean ± SD	
Hemoglobin	Control	10.94±0.96	11.13±1.05	P=0.45
	Study	10.92±0.95	1.28±1.01	P=0.15
Total Leucocyte Count	Control	9788±1630.	9586.84±1514.50	P=0.66
	Study	9720±1618.37	9634.23±1583.23	P=0.56
ESR	Control	11.68±1.38	11.54±1.60	P=0.69
	Study	11.36±1.21	11.66±1.47	P=0.35
Blood Urea	Control	20.70±2.40	20.84±2.54	P=0.83
	Study	20.56±2.33	20.88±2.82	P=0.63
Serum Creatinine	Control	0.77±0.13	0.77±0.12	P=0.86
	Study	0.76±0.13	0.78±0.13	P=0.30
SGOT	Control	17.64±4.52	17.51±4.04	P=0.90
	Study	17.88±4.36	17.43±4.38	P=0.72
SGPT	Control	12.02±4.03	18.04±4.58	P=0.36
	Study	16.72±4.14	17.78±5.17	P=0.30

P≤0.05 Significant; p≤0.01 highly significant; P=≤0.001 very highly significant.

Statistical analysis shows no significant difference in Hb, Total count, ESR, B Urea, S-creatinine, SGOT, and SGPT levels between study & control groups.

Therefore no significant change seen in both study and control groups regarding hematological and biochemical parameters during the study.

ECG & CXR and urine routine were also within normal study both at the start of the study and at the end of the study in both groups.

DISCUSSION

Diabetes Mellitus is becoming more common in both urban and rural population. Medical expenditures are high for treating diabetes mellitus and its complications[76]

[In spite of regular treatment, hyperglycemia goes unchecked in many patients.[77] Many drugs like sulphonylureas and thiazolidinedione's are not used optimally because side effects limit their use. Inventions of new drugs are increasingly needed in the treatment of diabetes mellitus.

Bromocriptine which is used in other conditions is found to be useful in diabetes mellitus. More studies are needed to evaluate the efficacy and safety of Bromocriptine in diabetic population of Tamilnadu. Hence this study was done to evaluate the efficacy and safety of Bromocriptine in patients with Diabetes mellitus coming to Diabetic outpatient department of Chengalpattu medical college and hospital, Tamilnadu.

In this study, diabetic patients were divided in to two groups. Patients received Bromocriptine of 1.6mg in addition to metformin and glipizide in the study group and the results were compared to that of control group who received only metformin and glipizide. The results of the study is discussed below:

DEMOGRAPHIC CHARECTERISTICS

Age distribution

When analyzed statistically and it is found there was no stastically significant difference between mean age of control and study group at baseline.

Sex Distribution

In the control group, total number of Males were 26, and total number of females were 32. In the study group, total number of Males were 29, and total number of females were 31.Sex distribution was stastically analysed.There was no stastically significant difference between of study and control group regarding sex distribution at the start of the study.

Body Mass Index [BMI]:

Mean BMI of control group was 26.36, mean BMI of study group was 26.03 at baseline and there was no stastically significant difference between mean BMI of study and control group at the baseline. [P=0.42].

In the control group the end of 3 months,BMI decreased from (26.36 to 26.1) about **0.26**[p=0.06].In the study group at the end of 3 months BMI decreased from(26.03 to 26.01) **0.02**.[p=0.19].Therefore, both the study and control group show decrease in the BMI after 3 months. The reduction is not statistically significant in both the groups.

Many studies by Meier et al, Cincotta et al shows weight loss caused by Bromocriptine[78,79]

Some studies show inconsistent results, such as studies by Pijl et al, Aminorroaya et al, Masada et al[80, 81, 82]..but weight gain is not caused by Bromocriptine in any of the previous studies.

In our study, result shows that there is only mild decrease in mean BMI which is not significant.

Effect on FBS

AT Baseline, the FBS of control group and study group did not display any statistically significant difference.

But, at the end of 3 months FBS shows DECREASE in FBS in both control [**23mg/dl]** and study [**48mg/dl]** groups. The decrease in FBS is stastically significant in both study [**P=0.0001]** and control groups. **[P=0.0001].** The decrease in FBS is higher in the study group than the control group.

Thus In this present study combination of Bromocriptine along with metformin and glipizide caused more reduction in FBS than combination of metformin and glipizide alone.

Previous Studies by Pijl et al[80], Shows there was a decrease in FBS to about 18mg/dl in Bromocriptine group patients. Previous studies by Ramatke at al[83]shows reduction in mean FBS in bromocriptine+Metformin group about 44.31mg/dl at 12 Weeks which was stastically significant.[$p<0.05$] .

EFFECT ON PPBS

AT Baseline, the PPBS of control group and study group did not display any statistically significant difference.

But, at the end of 3 months DECREASE in PPBS in both control [**29mg/dl**] and study [**76mg/dl]** groups was seen. The decrease in PPBS is stastically significant in both study [**P=0.0001]** and control groups. **[P=0.0001**]. The decrease in PPBS is higher in the study group than the control group.

Thus In this present study combination of Bromocriptine along with metformin and glipizide caused more reduction in PPBS than combination of metformin and glipizide alone.

Similar studies done by Ramteke at al [83]showed statistically significant reduction of PPBS About 43.71mg/dl at 12 weeks. [P<0.05] compared to baseline. Another study done by Kamath *et al*[84], shows the reduction in postprandial sugar was 16 mg/dl in the Bromocriptine group.

HbA1C

AT Baseline, mean HbA1C of control group and study group did not show any statistically significant difference.

But, at the end of 3 months this study shows DECREASE in meanHbA1C in both control [0.3%] and study [0.5%] groups. The decrease in mean HbA1C is stastically significant in both study [P=0.001] and control

groups. [P=0.0001]. The decrease in mean HbA1C is higher in the study group than the control group.

Thus In this present study combination of Bromocriptine along with metformin and glipizide caused more reduction in HbA1C than combination of metformin and glipizide alone.

Similar studies done by Ramatke at al[83], showed reduction in mean HbA1C to about 0.74% in the group treated with Bromocriptine compared to the other groups. [P< 0.05]. Also studies by Pijl et al[80] found patients on Bromocriptine group found a stastically significant reduction about 0.6% of HbA1c Compared to other groups.

Clinical conditions like obesity, insulin resistance, hypertension, and CKD reveal high NE plasma levels, sympathetic over activity, and hyperprolactinemia which in turn was due to reduced dopaminergic tone. Dopamine agonists such as Bromocriptine improve these clinical conditions[85, 86, 87, 88].

EFFECT ON LIPID PROFILE

In our study, fasting lipid profile [LDL, VLDL, HDL, TGL, TOTAL CHOLESTEROL] was done at the start and end of the study in both study and control groups.

The results show that there is stastically significant reduction in Total cholesterol in the study group [**p=0.0001**] and also in the control group. [**p=0.003**]. But the reduction was higher in the study group.

There is stastically significant reduction in LDL in the study group [**p=0.001**] but in the control group [p=0.7] no stastically significant reduction was seen at the end of the study.

There is stastically significant reduction in TGL in the study group **[p=0.001**] but in the control group [P=0.06] no stastically significant reduction was seen at the end of the study.

There was no stastically significant reduction in VLDL in the study group as well as in the control group seen at the end of the study. Also there is no significant increase in the HDL level in both control and study group when compared to baseline.

However there is no adverse effect of causing increase in blood lipid levels in study group and also in control group. Several anti-diabetic drugs such as rosiglitazone caused adverse effect on lipid profile. In our study, no adverse effect on serum lipid was found to be caused by Bromocriptine.

Similar studies were done to evaluate the effect of Bromocriptine on lipid profile.

Some studies showed a stastically significant results depicting decrease in fasting and post-prandial triglycerides by 72 and 63 mg/dl ($P < 0.005$) and fasting and post-prandial free fatty acids by 150 and 165 qr/l ($P < 0.05$), compared to placebo.[89]

Some other studies showed insignificant results when the effect of Bromocriptine on lipid profile is compared to placebo group[90].

Other hematological and biochemical parameters done at baseline and at the of 3 months show no abnormal effect on it caused by bromocriptine administration.

Monitoring for adverse events also showed no major life threatening adverse effects. Mild adverse effects like nausea, vomiting and hypoglycemia occurred during the study period. .There was no stastically significant difference between the adverse effects in the study and control groups.

So Bromocriptine quick release is a safe drug that can be used in type 2 Diabetesmellitus. It is available in India as tablet Bromocriptine Mesylate I.P equivalent to Bromocriptine 0.8 mg.

SUMMARY

The results of this randomized open labeled clinical trial throw light on the effect of Bromocriptine in diabetes mellitus

The results show in Type 2 Diabetes Mellitus, add on therapy of BROMOCRIPTINE QR to metformin and glipizide in the study group, when compared to the control group of patients receiving metformin and glipizide alone

Have caused

a) significant reduction in the Fasting blood sugar, Postprandial blood sugar,HbA1C

b) Significant reduction in Total cholesterol, TGL and LDL.

c) Significant reduction in systolic and diastolic BP.

There are no serious adverse effects observed in Type 2 Diabetes Mellitus patients taking Bromocriptine QR 1.6 mg OD.

CONCLUSION

The conclusion of this study is as follows

- Bromocriptine is effective in reducing fasting blood glucose, postprandial blood glucose and HbA1c.
- Bromocriptine also has favorable effect on BMI and lipid profile and blood pressure.
- Bromocriptine in doses used 1.6mg/day is found to be safe. No major adverse effects were seen during the use of Bromocriptine.
- Bromocriptine has advantages of not causing weight gain, and dyslipidemia and hypoglycemia.

Further large scale studies are necessary to highlight the effect of Bromocriptine on lipid profile and hypertension.

In Modern India, more drugs acting through multiple mechanism of action are necessary to challenge DM in the future.

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INSTITUTIONAL ETHICS COMMITTEE

CHENGALPATTU MEDICAL COLLEGE , CHENGALPATTU

APPROVAL OF ETHICAL COMMITTEE

To

Dr.M.Nithyapriya., D.Diab.,
MD Pharmacology
(2nd Year)
Chengalpattu Medical College,
Chengalpattu.

Dear Dr.

The Institutional Ethical Committee of Chengalpattu Medical College reviewed and discussed your application to conduct the clinical / dissertation work entitled

EFFICACY AND SAFETY OF BROMOCRIPTINE QR AS AN ADD ON THERAPY WITH METFORMIN AND GLIPIZIDE IN TYPE 2 DIABETES MELLITUS PATIENTS A OPEN LABELLED RANDOMIZED CONTROL STUDY.

ON 11.06.2014

The following documents reviewed

1. Trial protocol, dated _____version no
2. Patient information sheet and informed consent form in English and / or vernacular language.
3. Investigators Brochure, dated _____version
4. Principal Investigators current CV
5. Investigators undertaking

The following members of the Ethics committee were present at the meeting held on

Date 11.06.2014 Time 11.30 Noon Place Chengalpattu Medical College

Approved _____ Chairman Ethics Committee

_____ Member secretary of Ethics Committee.

Name of each member with designation:-

Clinical Members

1. Dr.R.Muthuselvan MD.,
   Prof & HOD of Medicine, CHMC

2. Dr.C.Srinivasan MD.,
   Prof & HOD of Surgery, CHMC

Biological Scientist

3. Dr.K.Baskaran MD.,
   Asso Prof of Pharmacology, CHMC

Non Clinical Member

4. Dr.P.Parasakthi MD
   Prof & HOD of Forensic Medicine,CHMC

5. Member from Nongovernmental
   Voluntary Organisation : Mr.P.Durairaj

6. Philosopher : Mr.K.S.Ramprasad

7. Lawyer : Lr. I. M. Karimala Basha

8. Layperson : Mr.Dilli

We approve the clinical trial to be conducted in its presented form

The Institutional Ethics Committee expects to be informed about the progress of the study and any SAE occurring in the course of the study, any changes in protocol and patient information / informed consent and asks to provide copy of final report.

Yours sincerely

11/6/14

Member secretary, Ethics Committee

INFORMATION TO PARTICIPANTS

Principal Investigator: - Dr.M.Nithyapriya D.Diab.,
MD Pharmacology Postgraduate
Chengalpattu medical College
Chengalpattu.

Nameoftheparticipant: -

_____

Title : **EFFICACY AND SAFETY OF BROMOCRIPTINE QR AS AN ADD ON THERAPHY WITH METFORMIN AND GLIPIZIDE IN TYPE 2 DIABETES MELLITUS PATIENTS an OPEN LABEL RANDOMIZED CONTROLLED STUDY**

This study is conducted in our institution, Chengalpattu medical College, Chengalpattu.

You are invited to take part in this study. The information in this document is meant to help you to decide whether or not to take part. Please feel free to able if you have any queries or concerns.

You are being asked to participate in this study conducted in the department of general medicine and department of pharmacology, Chengalpattu Medical College.

Purpose of research:

To do a study of efficacy and safety of Bromocriptine QR as an add on therapy to diabetic treatment metformin, glipizide in Type 2 Diabetic mellitus patients.

The study is conducted with permission from the Institutional ethical committee.

Study design : Randomized control study.

Study Procedure

The study involves laboratory investigations including blood glucose estimation and regular clinical assessment of patient's recessing the new drug Bromocriptine QR for a period of 3 months.

Bromocriptine QR 1.6 mg tablets will be given to take once daily in the morning.

Periodic assessment of blood glucose levels will be done at the start of therapy and regular monthly intervals and at the end of the study (3 months. You will be asked to review at regular intervals. At each visit the doctor will examine you.

In addition, if you notice any physical or mental change, you must contact the persons listed at the end of the document.

You may have to come to hospital for examination and investigations apart from your scheduled visits if required.

You must not participate if you are pregnant, breast feeding a child or suffering from any serious medical illness like coronary artery disease, kidney or liver disease, cancer or any surgical illness.

Benefits of the study :

The results of the research may provide benefits to the society in term of thereauptic advancements in diabetic patients and benefits future of diabetic patient's. It helps to reduce the burden of diabetes in our society.

jfty; gbtk;

Kjd;ik Ma;thsh; : kUjJth. k. e;jag;h;ah›
nrqfyglL kUjJtf fyY}h;

gq;F ngWgth;d; ngah; :-
.....

ji;ygG : rhffiu Nehahs;fs;d ,ujj rhffiu msit FiwfFk GNuhNkhf;h;gbd vdw kUej;d jdikiaAk› mjd ekgfjjdikiaAk mw;tJ Fw;jJ eljjggLk MaT.

,ej MaT nrqfyglL muR kUjJtkida;d eh;oT Neha r;f;rif g;h;t;y› eljjggLf;wJ. ,ej MaT kUjJth k. e;jag;h;ah mthfshy mDgtk thaej kUjJthfs;d cjt;NahL eljjggLf;wJ.

Ma;t;d; Nehf;fk

nghJthf rhffiu Nehahs;fs vLjJfnfhsSk kUejhdJ› gfft;isTfis czlhfFtjhf cssJ. ,jidf fUjj;y nfhzLk› rh; nraAk Kawr;ahfTk ,ej GNuhNkhf;h;gbd vdw kUeij gadgLjj; rhffiu Nehia FzggLjJtj;y› Mgjjhd gfft;isTfs ,yyhky rhffiuia Fiwff ,ej MaT eljjggLf;wJ.

Ma;Tf;fhd nray; Kiwfs;

rhffiu Nehahs;fSfF› rhffiu Nehaffhd kUeJfSld› GNuhNkhf;h;gbd vdw kUeJ toqfggLk.

GNuhNkhf;h;gbd vdw kUej;id 1.6 k;yy;f;uhk vdw mst;y› j;dKk xUKiw fhiya;y clnfhss NtzLk.

,ej kUej;id clnfhsSk rhffiu Nehahs;fSfF› ,uzL thuj;wF xUKiw rhffiu msit gh;Nrhj;ggjwfhf› ,ujj gh;Nrhjid Nkwnfhssggk.

mJklLkyyhky› nkhjj cly gh;Nrhjidak eljjggLk. Eiuauy› fyyuy› r;Weufk Mf;atww;d nrayghlbid mw;tjwfhd r;wgG ,ujjgh;Nrhjidak nraaggLk. MaT eljjggLk fhyk 3 khjqfs.

xtnthU tUifapYk rhffiu Nehahspfs> kUjJtuhy rpwgghf ftdpffggLthhfs.

GNuhNkhfphpgbd kUejpid clnfhsSk rhffiu NehahspfSfFk kUejpid vLjJf nfhsshj rhffiu NehahspfSfFk ,ilNaahd rhffiu mstpd flLgghL tpjjpahrjij mwpa ,ej MaT cjTk. ,ej Matpy gqnfLjJfnfhssTk> gadgLjjpf nfhssTk rhffiu Nehahspfs NflLfnfhssggLfpwhhfs.

,ej Matpy Ra tpUggjJld gqNfwf Kdtejhy klLNk fyeJfnfhss KbAk. Matpy gqnfLjJfnfhsSk rhffiu Nehahspfspd nrhej tpguqfs vJTk ntspapIggl khllhJ.

NehahspfSfF VwgLk vejtpjkhd njhejpuTfisAk kUjJthplk njhptpffyhk. mjwfhd rpfprir clNd toqfggLk.

fhggpzp ngzfs> jhagghy GflLk ngzfs ,ej Matpy fyeJfnfhssf $lhJ.

,Uja Neha> rpWeuf Neha> fyyuy Neha Mfpatwwhy ghjpffgglthfSk> rkgjjpy mWit rpfprir nraJf nfhzlthfSk ,ej Matpy gqNfwf $lhJ. ,ej Matpd KbTfs midjJk> gqFnfhzl rhffiu Nehahspfs midtUfFk njhptpffggLk.

,ej Matpid eljJtjwF kUjJtkidapd Kiwahd mDkjp ngwgglLssJ.

,ejMatpd;gadfs;

rhffiu Nehahspfspd vjphfhy thofif Kiwapy eyy KdNdwwk VwglTk> ,eNehahy rKjhajjpYk> FLkgjjpYk VwgLk ghjppgpid FiwffTk ,ej MaT cjTk.

,ejpahtpy rhffiu Nehahspfspd vzzpfif mjpfkhfpf nfhzNl tUfpwJ. ,jid flLggLjj gyNtW Gjpa kUeJfis gadgLjJtJ mtrpakhfpwJ. ,ej MaT mjwF toptFfFk.

Mathshpd ifnahggk gqFngWk Nehahspapd ifnahggk

ehs :

,lk :

INFORMED CONSENT FORM

(This is only a guideline –Relevant changes to be made as per the study requirements)

Title of the study : **EFFICACY AND SAFETY OF BROMOCRIPTINE QR AS AN ADD ON THERAPHY WITH METFORMIN AND GLIPIZIDE IN TYPE 2 DIABETES MELLITUS PATIENTS; AN OPEN LABEL RANDOMIZED CONTROLLED STUDY**

Name of the participant :

_____

Name of the Investigator : Dr.M.Nithyapriya

Name of the Institution : Chengalpattu Medical College Hospital

Documentation of the informed consent.

I _____have read the information in this form (or it has been read to me).I was free to ask any questions and they have been answered. I am over 18 years of age and, exercising my free power of choice, hereby give my consent to be included as a participant in '**efficacy and safety of Bromocriptine QR as an add on therapy with Metformin and Glipizide in type 2 diabetes mellitus patients; an open label randomized controlled study'**

1. I have read and understand this consent form and the information provided to me.
2. I have had the consent document explained to me.
3. I have been explained about the nature of the study.
4. I have been explained about my rights and responsibilities by the investigator.
5. I have been informed the investigator of all the treatments I am taking or have taken in the past_____including any native (alternative) treatment.

6. I have been advised about the risks associated with my participation in this study.
7. I agree to cooperate with the investigator and I will inform him/her immediately if I suffer unusual symptoms.
8. I have not participated in any research study within the past_____.
9. I have not donated blood within the past_____- Add if the study involves extensive blood sampling.
10. I am aware of the fact that I can opt out of the study at any time without having to give any reason and this will not affect my future treatment in this hospital.
11. I am also aware that the investigator may treatment my participated in the study at any time for any reason, without my consent.
12. I hereby give permission to the investigators to release the information obtained from me as result of participation in this study to the sponsors, regulatory authorities, Govt.Agencies, and IEC. I understand that they are publicly presented.
13. I have understood that my identity will be kept confidential if my data are publicly presented.
14. I have had my questions answered to my satisfaction.
15. I have decided to be in the research study.

I am aware that if I have any question during this study, I should contact the Investigator. By signing this consent form I attest that the information given in this document has been clearly explained to me and understood by me, I will be given a copy of this consent document.

For adult participants:

Name and signature/thumb impression of the participant (or legal representative if participant incompetent)

Name_____signature_____
_____Date_____

Name and signature of impartial witness (require for illiterate patients)

Name_____signature_____
_____Date_____

Address and contact number of the impartial witness:

_____
_____

Name and signature of the investigator or his representative obtaining consent:

Name_____signature_____
_____Date_____

For children being enrolled in research:

Whether child's assent was asked: Yes/No

(If the answer to be above question is yes, write the following phrase:

You agree with the manner in which assent was asked for from your child and given by your child. You agree to have your child take part in this study.

(If answer to be above question No, give reason: _____

Although your child did not or could not give his or her assent, you agree to your child's participation in this study.

Name and signature of/thump impression of the participant's parent(s) (or legal representatives)

Name_____signature_____
_____Date_____

Name_____signature_____
_____Date_____

Name and signature of impartial witness (require for parents of participant child illiterate):

Address and contact number of the impartial witness: _____

_____

Name and signature of the investigator or his representative obtaining consent:

Name_____signature_____
_____Date_____

NOTE:-

For observational studies in nature or those in which only patient's tissue, body fluids are collected for any kind of analysis the following elements in the patient information leaflet will need be included – background of the study the purpose for which the sample will be used: confidentially of data are right to refuse to give specimens should be included. Points 6, 7,8,9,10,11 of consent document may be excluded in such cases.

xgGjy; gbtk;

j‰U/j‰Ukj‰.....
.....
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.....

t‰yhrjj‰y tr‰fFk ehd› vdfF ms‰ffggll jfty gbtjj‰y css t‰raqfis gbjJk› NflLk Gh‰eJf nfhzNld.

,ej MaT kUjJth. k. e‰jag‰h‰ah mthfshy› mDgtk thaej kUjJthfs‰d cjt‰NahL nrqfyglL mu‰R kUjJtkid› eh‰o‰T Neha r‰f‰rir g‰h‰t‰y eljjggLf‰wJ vdgij mw‰Ntd.

‘GNuhNkhf‰h‰gbd’ kUeJld› eh‰o‰T Nehaffhd kUeJk cld toqfggLk vdgij njh‰eJf nfhzNld.

,ej Mat‰wF Njitahd ,ujjg gh‰Nrhjidf SfF› clgl rkkj‰ff‰Nwd.

Mat‰y njhlheJ gqFngw t‰Uggk ,yiy vdwhy t‰yf‰fnfhssyhk vdWk mw‰eJfnfhzNld.

Mat‰d Kbt‰id nrhej milahsqfis nts‰a‰lhky kUjJt Muharr‰ffhf gadgLjj‰f nfhss rkkj‰ff‰Nwd.

ehs : ifnahggk :

,lk : ngah :

PROFORMA

Name: Age: Sex: Hospital No:

Weight :

Present History :

Past History :

Treatment History :

General examination :

Temperature :

Anemia :

Lymphadenopathy :

Pedal edema :

Jaundice :

Pulse Rate :

Blood Pressure :

Lab investigations :

Systemic examination:

- CVS
- RS
- Abdomen
- CNS

Investigation	At the start of therapy	At the end of 8 weeks
Hb% Total count Differential count ESR Blood sugar Blood urea Serum creatinine Lipid profile:		

Total cholesterol LDL HDL TG VLDL Urine routine Urine ketone Chest xray ECG		

Blood glucose estimation:

Blood glucose	**Week**				
	Basal	**2nd**	**4th**	**6th**	**8th**
Fasting					
Post prandial					

DIET CHART

Name	:	Ht	:	Cms
Age	: Yrs. :	Wt	:	Kg
Sex	: Male / Female	BMI	:	
Date	:	Energy	:	Kcals

உணவு முறை / MEAL PLANNING

நேரம் Time	உணவு வகைகள் Menu	1600 Kcals	1800 Kcals
6.00 மு.ப. A.M.	டீ அல்லது காபி சர்க்கரை இல்லாமல் பாலுடன் (ஏடு இல்லாமல்) Tea or Coffee without Sugar / Horlicks Lite	100 ml	100 ml
8.00 மு.ப. A.M.	இட்லி அல்லது / Idly or	4	5
	தோசை அல்லது / Dosai or	3	3
	சப்பாத்தி அல்லது / Chappathi or	4	4
	உப்புமா / Uppuma or	2 Cup	2 1/2 Cup
	பொங்கல் சட்னி (அ) சாம்பாருடன் (தேங்காய் இல்லாமல்) Pongal with Chutney or Sambar (Avoid Coconut)	150 ml	150 ml
	Vegetables (சிறுங்கு இல்லாமல்)	50 gm	50 gm
11.00 மு.ப. A.M.	மோர் / Butter Milk	100 ml	100 ml
	2 ஹார்லிக்ஸ் லைட் பிஸ்கட் / Horlicks Lite Bite Biscuit 2	2/100 ml	3/150 ml
	காய்கறி சூப் / Vegetable Soup / பச்சை காய்கறிகள் / Vegetable Salad /	100 gm	100 gm
	பழம் / Fruit	75 gm	75 gm
1.00 பி.ப. P.M.	சாதம் / Rice	2 Cup	2 1/2 Cup
	கீரை / Greens	100 gm	100 gm
	காய்கறிகள் / Vegetables.	100 gm	100 gm
	சாம்பார் / Sambar	150 ml	150 ml
	கோழிக்கறி (அ) மீன் / Chicken or Fish	70 gm	70 gm
	மோர் / Butter Milk	100 ml	100 ml
	ரசம் / Rasam	50 ml	50 ml
5.00 பி.ப. P.M.	டீ (அ) காபி சர்க்கரை இல்லாமல் பாலுடன் (ஏடு இல்லாமல்) Tea or Coffee without Sugar with milk (Skimmed)	100 ml	100 ml
	2 ஹார்லிக்ஸ் லைட் பிஸ்கட் / 2 Horlicks Lite Bite Biscuit	3	3
	சுண்டல் / Sundal / உப்புமா / Uppma	1/2 Cup	3/4 Cup
8.00 பி.ப. P.M.	சாதம் / Rice / உப்புமா Uppma அல்லது	2 Cup	2 1/2 Cup
	சப்பாத்தி / Chappathi (எண்ணெய் இல்லாமல்) (Dry)	4	4 - 5
	இட்லி / தோசை Idly / Dosai		
	காய்கறிகள் / Vegetables	100 gm	100 gm
	பருப்பு / Dhall	50 ml	50 ml
	ரசம் / Rasam	50 ml	50 ml
10.00 இரவு P.M.	பால் / Milk (சர்க்கரை இல்லாமல்) (without sugar) / Horlicks Lite / ஹார்லிக்ஸ் லைட்	75 ml	75 ml

ஒரு நாள் முழுவதும் சமையலுக்குரிய எண்ணெய் அளவு 2 - 3 tsp

CONTROL GROUP																													
ent num	age	gender	MI befo	hba1c	fbs0	ppbs0	fbs1	ppbs1	fbs2	ppbs2	fbs3	ppbs3	BMI END	hba1c en	L CH BE	TAL CH	GL BEFO	GL AFTE	L BEFOR	LDL A	DL BEFO	DL AFTE	DL Befo	LDL Afte	SBP B	SBP A	DBP B	DBP A
1	42	F	26.4	8	210	350	196	322	290	180	190	300	26	7.6	250	253	198	197	73	77	39	38	39	36	150	130	90	80
2	50	F	22.1	6.8	146	279	142	220	146	270	130	262	22	7	200	204	185	188	154	154	48	50	29	28	130	130	90	90
3	53	M	27	7	136	196	127	204	140	211	136	179	27	6.3	209	209	194	193	100	103	34	38	73	70	110	110	80	70
4	48	F	24	7	124	208	114	180	119	209	124	190	24	7	230	234	210	209	187	187	55	49	26	28	130	120	80	80
5	56	F	24.6	7.5	260	380	254	348	204	276	213	298	24.4	7	212	202	168	166	176	174	40	49	42	38	140	130	80	80
6	43	M	21.8	7	164	229	116	249	210	240	121	180	21.4	6.7	300	302	158	156	243	241	45	40	32	34	140	130	90	80
7	53	M	29.6	9	229	340	230	320	172	298	216	348	29.6	8.6	277	273	172	173	158	158	38	37	28	30	150	140	100	80
8	47	M	30	7.5	210	299	196	289	156	242	180	200	29	7	193	199	188	187	156	156	20	24	41	39	148	140	90	90
9	57	M	25.6	7.5	166	246	142	223	110	180	140	197	25.5	7.5	178	177	194	197	167	167	28	25	21	25	120	110	80	70
10	49	F	24	7	130	210	124	199	132	240	130	302	26	7.5	212	212	138	132	156	156	39	36	45	44	110	110	80	70
11	57	M	25.7	7.5	156	254	148	266	136	250	144	242	24.8	7.3	298	289	138	137	98	98	50	45	65	62	116	130	80	90
12	56	M	25	7.5	118	286	119	263	180	266	145	290	26	7.3	322	321	145	143	96	100	51	45	55	48	110	110	70	70
13	61	F	26.8	8	220	310	204	340	209	280	280	360	28	8	187	183	170	173	176	176	26	27	44	40	120	110	70	80
14	44	F	28.3	9	259	349	255	316	204	346	250	310	24	8.7	178	177	147	146	154	154	62	61	105	79	110	110	70	70
15	55	F	24.1	7.5	160	270	155	210	140	250	155	250	22	7	189	187	181	180	165	165	32	34	30	33	120	120	76	84
16	52	M	22.3	7	165	240	165	224	160	292	145	220	22	6.7	167	162	225	224	167	167	54	54	61	57	150	140	100	80
17	38	F	22.9	7	140	236	136	232	133	199	120	180	23	6.4	176	178	210	209	154	154	37	45	29	26	130	130	90	80
18	59	F	23	7	126	204	130	194	140	186	114	182	25	6.5	203	206	235	234	87	84	26	18	46	42	150	140	100	80
19	57	F	25	6.8	138	210	121	177	110	155	119	145	26	6	276	278	180	182	187	188	42	33	35	47	130	130	80	90
20	60	F	27.3	7.5	148	269	149	196	120	195	120	190	26	7	269	266	170	169	183	185	48	46	30	35	130	138	90	88
21	55	M	26	7.5	192	286	109	270	166	240	140	240	24	7.2	276	270	167	166	155	155	39	35	32	65	128	130	84	80
22	54	F	24	7	154	240	146	286	120	210	126	186	22	6.5	244	246	212	211	154	159	28	28	57	47	130	120	80	70
23	49	F	22.4	7	124	206	128	180	127	190	119	180	22	6.8	213	212	169	165	172	171	47	46	190	180	130	130	80	90
24	54	M	27.5	7.5	190	260	182	262	176	245	160	204	27	7.2	288	287	138	138	211	201	48	45	44	45	130	130	80	90
25	57	M	28	7.5	180	274	210	266	289	347	180	266	28	7.5	294	290	145	144	201	201	37	37	46	45	130	130	80	80
26	51	M	32.1	8.5	210	302	202	290	300	380	249	356	32	8.6	289	284	177	178	129	129	35	35	46	47	150	130	100	80
27	53	M	30.6	8.5	252	379	242	344	206	411	210	288	30	7.6	325	321	172	176	165	170	38	37	50	51	150	130	100	80
28	58	M	22	7	170	260	140	286	180	260	140	264	22	7	289	287	171	171	212	212	42	43	38	35	130	130	80	80
29	42	F	27	9.5	316	402	280	350	280	364	290	354	27	8.8	234	231	148	147	134	134	38	36	40	39	110	110	70	70
30	54	F	28.9	9	280	364	270	325	240	290	186	350	29	8	211	215	205	204	123	123	44	44	32	33	130	130	90	80
31	51	M	25	7	196	270	200	263	189	266	172	202	25	7	190	187	187	186	124	124	40	40	27	27	140	130	80	80
32	54	F	23.9	7	142	196	140	192	131	166	127	190	24	6.5	235	223	201	203	143	143	47	45	59	55	130	128	90	86
33	51	F	27	7.5	206	280	180	206	144	210	154	262	27	7.4	276	278	206	205	167	167	36	36	25	25	110	110	70	70
34	48	F	28.4	7.5	196	246	199	340	170	241	135	236	28	7.6	245	243	175	177	212	212	50	55	35	35	120	110	80	70
35	58	F	29.6	8	210	314	204	304	190	290	170	260	29.6	7	255	254	166	165	221	221	42	42	33	32	130	130	80	80
36	52	M	27.6	8.1	176	256	163	219	188	285	187	255	28	8	289	284	175	175	176	176	49	49	34	33	140	130	90	80
37	56	M	27.4	8	200	320	194	310	191	296	175	306	26	8	278	277	175	174	167	167	39	39	35	35	140	130	90	80
38	52	F	26.2	7.5	164	272	170	258	210	260	155	255	25	7.4	211	212	209	208	154	154	25	29	26	23	140	130	90	88
39	56	M	25	7.5	144	290	126	280	144	275	131	289	27	7.2	278	274	210	211	149	149	27	27	40	40	110	110	70	80
40	53	M	28.9	7	128	220	124	210	110	185	120	190	28.4	7	189	187	145	145	178	178	37	35	60	62	110	120	70	80
41	37	F	28	7.5	220	366	210	376	204	362	180	344	28	7.5	218	213	146	147	121	121	48	48	34	34	120	130	80	90
42	65	F	24.3	7	142	249	146	230	125	199	126	186	24	6.5	267	265	157	156	145	145	49	54	39	33	120	110	70	70
43	40	F	23	7.5	158	254	156	224	141	192	130	176	23	7.4	215	213	190	188	176	176	25	29	65	65	110	110	80	80
44	63	M	26.7	8.5	266	380	244	376	260	360	240	309	25.3	8	180	176	158	154	187	187	60	65	35	35	110	110	80	80
45	55	F	25.3	7	186	230	170	226	160	204	114	155	25	6.5	276	277	210	202	198	196	38	38	54	54	120	130	80	84
46	50	M	27.2	7.5	176	269	162	254	145	290	170	282	27	7.5	329	332	235	220	178	178	52	52	28	24	140	130	90	80
47	40	F	25	7.5	162	222	155	281	142	205	126	190	25	7	309	306	208	209	167	167	34	33	37	37	130	130	80	80
48	46	M	29.2	9.5	230	402	220	386	210	335	180	320	29	8.5	232	231	237	237	178	173	20	20	53	54	140	130	90	80
49	62	M	28.6	7.5	176	264	174	210	165	270	164	259	28	7.5	287	285	183	189	179	173	44	46	32	32	130	130	90	90
50	50	F	27.5	7.5	209	304	210	272	180	304	170	280	27.3	7	276	270	169	166	143	143	47	44	30	30	130	138	80	88
51	54	F	29.2	8.5	306	380	290	368	310	406	291	372	31	8.4	222	221	173	132	157	151	34	34	44	42	130	130	80	80
52	58	M	28.7	7.5	196	279	184	273	190	263	178	266	28	7.5	256	254	210	211	178	178	25	25	67	65	120	120	70	70
53	61	F	25.9	7.5	180	254	174	248	187	234	172	231	25	7.2	287	290	175	177	178	178	45	43	43	43	130	130	90	90
54	49	M	26	8.7	216	360	242	352	244	370	190	355	26.2	8.5	232	232	140	141	187	187	47	47	30	30	130	130	90	90
55	61	F	27.4	8.5	242	332	220	332	200	290	142	280	27	7.5	211	213	147	145	184	184	36	36	45	45	130	130	80	80
56	51	M	24.8	7	158	246	150	290	148	264	140	226	24	7	298	296	180	182	178	178	34	34	54	53	140	110	90	80

57	64	F	28.4	7	182	253	178	246	109	170	126	155	28	6.4	176	181	177	173	186	178	36	36	36	33	140	130	90	80
58	52	M	27	7.5	220	281	216	290	240	266	148	267	27	7	243	240	145	144	134	145	40	43	42	40	130	130	80	80

STUDY GROUP																														
ent nun	AGE	GENDER	MI Befo	A1C bef	FBS0	PPBS0	FBS1	PPBS1	FBS2	PPBS2	FBS3	FBS3	BA1C EN	BMI END		TC AF	TGL BF	TGL AF	LDL BF	LDL AF	HDL BF	HDL AF	VLDL BF	VLDL AF	SBP BF	SBP AF	DBP BF	DBP AF
1	41	F	25.4	7.5	205	340	190	325	175	305	154	276	7	25	287	260	148	132	205	198	50	48	20	19	130	130	90	90
2	60	F	26.8	7	187	218	170	205	142	190	126	210	6.4	26.8	360	343	216	203	187	185	48	50	38	37	150	130	110	100
3	52	M	23.9	7.5	183	340	179	331	190	298	154	280	7	22.9	255	250	175	155	201	194	40	38	29	29	140	120	100	90
4	53	F	24	7	192	252	184	242	179	241	146	204	6.5	24	278	262	179	152	206	210	41	39	26	25	130	130	90	80
5	35	F	29.4	8	234	366	240	350	210	340	143	214	7.5	29.4	265	260	185	192	175	168	49	48	26	27	130	130	80	80
6	59	F	26	8	193	298	191	270	170	256	136	209	7.6	26	278	269	197	180	166	158	48	48	30	32	120	120	80	80
7	43	M	24	7	166	208	116	206	117	190	104	162	6	24	297	280	266	265	175	161	49	50	52	48	130	130	80	90
8	51	F	23.8	6.8	156	221	104	224	91	207	90	175	6.6	23.8	301	296	186	165	175	172	42	44	37	34	110	110	70	70
9	44	M	28	7	110	234	112	220	114	190	106	142	6.5	28	266	255	186	178	209	188	30	28	38	35	130	130	80	80
10	56	M	27.8	7.5	128	257	138	247	140	280	127	190	7	27.8	210	218	153	152	210	194	20	22	30	31	110	110	80	70
11	55	M	30.2	8	275	397	280	387	254	340	186	263	7.5	30.2	273	270	170	171	145	138	45	44	30	28	114	110	70	70
12	65	M	22.9	8.5	182	362	186	342	170	304	142	290	8	22.9	225	220	221	217	146	138	38	40	40	41	110	110	70	70
13	58	F	23.8	7	188	285	114	267	105	243	102	198	6.6	23.8	268	259	186	190	157	145	30	28	20	22	110	110	80	70
14	61	F	24	7.5	225	342	210	302	191	294	153	208	6.9	24	271	265	221	201	190	170	35	33	25	23	140	140	90	90
15	57	F	28	7.6	192	354	172	350	174	332	136	290	7.2	28	272	267	232	197	158	147	44	41	39	38	130	130	80	80
16	57	F	26.8	7	150	272	148	280	134	270	117	210	6.8	26.8	225	220	174	166	210	181	41	43	30	29	130	130	88	90
17	30	M	27	7.8	148	335	132	320	126	307	114	230	7.2	27	280	282	270	251	235	225	19	18	69	58	130	130	80	80
18	51	M	24	8	224	303	241	315	210	305	186	294	7.8	24	241	238	140	132	208	210	18	19	28	25	138	130	90	90
19	60	F	29.6	8	148	302	151	288	132	276	124	209	7	29.6	250	247	182	158	240	235	34	33	54	49	110	110	70	80
20	47	F	28.7	8.5	256	372	240	315	213	342	153	256	8.1	28.7	242	241	168	159	186	180	30	32	49	47	120	120	80	80
21	61	M	27	8	182	249	172	328	140	283	127	195	7	27	260	261	178	154	169	170	35	37	32	29	140	130	90	80
22	55	F	24	6.5	162	204	104	198	111	180	107	146	6.2	24	234	233	171	192	173	167	32	33	48	47	130	130	80	80
23	42	M	24.8	7	187	243	114	213	118	196	112	144	6.7	24.8	250	252	183	165	210	212	31	35	35	34	110	110	70	70
24	55	F	25	7	154	245	87	241	108	264	104	168	6.5	25	285	280	154	113	175	169	36	37	30	29	120	120	80	80
25	57	M	26.9	7.5	198	389	163	362	141	353	126	287	7	26.9	264	260	180	163	140	138	47	49	28	30	130	130	90	90
26	62	M	26	7.5	180	277	130	260	112	264	104	208	7.2	26	234	250	156	158	147	145	47	46	29	35	130	130	80	80
27	38	M	23	7.5	132	371	111	350	126	360	115	314	7	23	242	212	184	170	180	177	45	44	40	41	130	130	80	80
28	53	F	27.5	7	142	296	132	287	112	265	114	226	6.6	27.5	233	240	187	179	177	172	46	47	42	40	110	110	70	70
29	59	F	28.6	7.5	198	332	187	322	170	315	128	276	7	28.6	250	243	193	181	145	171	40	41	40	38	110	110	80	80
30	45	M	24.4	8	201	382	210	395	193	382	172	296	7.5	24.4	229	227	190	178	156	148	39	41	39	42	120	120	70	70
31	56	M	23.8	7	142	196	132	210	126	194	119	162	6.5	23.8	262	241	111	88	185	160	47	48	21	20	130	130	80	80
32	39	F	23.9	7.5	182	352	168	296	154	280	135	241	7	23.9	303	294	181	175	170	178	52	50	35	36	140	130	90	90
33	63	F	28.8	8	182	348	180	330	152	298	119	217	7	28.8	245	232	140	130	180	155	39	40	28	27	130	120	80	80
34	52	F	26.1	8.4	146	332	132	326	158	296	140	212	7.5	26.1	250	253	140	135	207	201	35	32	26	27	130	130	80	80
35	40	F	27.2	7.5	189	262	143	190	136	193	117	153	7.5	27.2	258	255	190	196	153	146	50	49	25	24	130	130	80	80
36	55	M	23	7.1	148	250	132	210	126	209	122	167	7	23	270	237	171	166	160	152	46	48	33	31	120	120	90	90
37	55	M	24.8	7.5	182	306	172	310	154	290	131	214	7	24.8	279	278	260	258	159	164	52	50	53	49	130	130	90	90
38	60	F	29	9.2	216	428	196	365	172	345	186	344	7	29	280	240	148	138	158	143	40	36	33	31	110	110	70	70
39	41	M	27.2	8.4	240	316	171	280	243	310	204	290	8.2	27.2	249	232	164	162	179	163	32	30	37	35	130	130	80	80
40	56	M	22.8	7	142	216	122	190	114	186	104	145	7.5	22.8	211	207	130	127	171	160	24	25	33	28	110	110	70	70
41	65	F	25	8	146	302	160	290	142	278	114	186	6.6	25	261	242	169	163	127	121	46	42	31	29	110	110	70	70
42	43	M	24.9	8	182	244	171	234	163	220	127	189	7.5	24.9	218	214	212	217	129	117	42	40	40	39	110	110	70	70
43	42	F	26	7.8	186	312	210	320	204	296	172	253	7	26	258	254	193	195	138	120	30	33	24	25	110	110	70	70
44	58	F	25.6	7	146	248	126	209	132	196	126	163	6.5	25.6	258	230	196	181	168	159	37	36	21	25	140	130	80	80
45	63	M	28.6	9	216	382	260	380	243	365	204	310	8.5	28.6	237	193	182	176	150	120	43	47	35	36	130	130	80	80
46	46	M	30	8.1	189	328	176	313	142	283	123	208	7.3	30	198	210	155	118	164	151	44	45	25	27	130	130	80	80
47	44	M	24	7.5	184	306	165	280	143	276	128	225	7	24	285	280	228	180	201	199	20	18	54	57	130	130	80	80
48	40	F	27	8.3	208	396	210	380	192	340	182	298	8.1	27	235	229	112	110	195	192	21	22	27	25	130	130	80	80
49	54	F	23	7	180	249	160	231	153	216	112	182	6.5	23	242	235	150	160	207	179	31	32	52	50	110	110	80	80
50	65	F	25.2	7.5	174	306	162	280	150	263	132	208	7	25.2	237	230	161	163	172	169	34	33	48	48	130	120	80	70
51	64	M	25	7	169	306	143	296	123	260	116	256	7	25	257	252	122	110	158	151	33	32	27	35	140	130	80	80
52	44	M	27.6	7.1	184	328	170	330	142	298	153	380	6.5	27.6	234	230	197	205	159	160	35	37	44	47	130	130	80	80
53	57	M	26	6.6	148	206	121	186	114	143	106	132	6	26	249	243	170	163	222	214	34	35	32	31	110	110	70	70
54	53	F	28.6	9	269	348	258	380	232	366	160	353	7.7	28.6	278	275	95	83	165	161	36	38	31	35	120	120	80	80
55	45	M	26	7	153	278	142	270	136	243	121	209	6.8	26	262	253	147	130	142	138	50	50	29	32	130	130	80	80
56	60	F	25.5	7.2	146	303	132	280	121	273	116	210	6.5	25.5	245	230	149	144	138	134	47	46	37	33	130	130	80	70
57	41	M	26	6.5	156	215	108	154	97	148	95	132	6.4	26	210	220	163	150	163	160	41	41	39	41	130	130	80	80
58	51	F	24.8	7	141	215	123	207	119	182	108	143	6.4	24.8	230	225	160	148	169	166	48	45	42	43	110	110	70	70
59	59	M	26.5	7.5	198	298	137	254	127	264	115	196	7	26.5	240	239	182	170	137	134	39	38	37	39	110	110	80	70
60	50	F	28.7	7	167	247	110	190	117	173	104	132	6.5	28.7	225	220	160	162	138	145	42	42	40	37	120	120	70	70